Evidence Based Management of Cancers in India

Guidelines for Imaging in Oncology

PART B

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Preface

This year marks the 12th "Evidence-Based Management" meeting at Tata Memorial Centre. Evidence-based medicine (EBM) has been defined as the use of current best evidence to make informed clinical decisions for individual patients. The Tata Memorial Centre has pioneered the concept of EBM in oncology in India and has been conducting the annual meeting on EBM in common cancers for the past 11 years. The focus of this year's meeting is on "Oncologic Imaging"

Inspite of considerable and rapid advances in imaging, radiology has lagged behind other clinical branches as far as evidence based practice is concerned because of lack of well-designed outcomes oriented studies. It is imperative to have a pragmatic view regarding the use of modern technological advances in the field of imaging. The most important aspect in imaging is about technology assessment, judging the accuracy of a technique and evaluating its impact in clinical practice. This needs to be studied in well designed trials.

While such data may not be available in many areas of oncologic imaging, the aim of this book and the meeting is not only to collate the existing evidence but also to identify areas where the evidence is lacking and formulate trials for future which can generate such evidence.

In oncologic imaging there is a need to evolve uniform practice guidelines that will lead to efficient use of resources and better clinical outcomes especially taking into consideration the Indian scenario. This book is an attempt to provide such guidelines based on scientific evidence and will serve as a useful tool for practicing radiologist.

R A Badwe
Director,
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February 2014
Mumbai

Evidence Based Radiology

The first paper concerning evidence based practice of Radiology was published in Lancet in 1997 entitled 'Medicine in 21st Century" authored by Hillman B J [1]. In 1999 'Radiology' published the second paper about Evidence Based Medicine and radiology "What is the Evidence?" authored by Woods B P [2], and then a review was published in 'Radiology' in 2001 titled 'Evidence Based Radiology: A New Approach to the Practice of Radiology' written by Evidence-Based Radiology Working Group [3], it outlined the concept of evidence based medicine in the field of radiology.

Radiology has made rapid progress with advances, in all imaging modalities, this has changed the face of radiology. Inspite of this, evidence based radiology is lagging in comparison to other clinical branches, as far as evidence based practice is cocerned. Evidence Based Radiology can be best described as selecting the appropriate imaging study with appropriate imaging protocol, based on the available clinical inputs, best available evidence, and radiologist's expertise and

patient's expectations. The discipline of radiology where two competing imaging modalities are compared is not as straight forward as comparing two treatment modalities, typically between a new drug and standard of care or between a new drug and placebo, to that extent randomised controlled trials in radiology may not be possible.

An assessment of the technology used, plays a very important role, thorough knowledge of technology used is necessary to implement it, in clinical settings and to evaluate its impact. Using improperly or inadequately designed imaging study, directly leads to under estimation of the diagnostic performance of the imaging modality. Both the technical performance and the diagnostic performance are important and must be assessed and in such situations technical expertise is as crucial as clinical expertise, in practice of Evidence Based Radiology. In addition, one needs to be conversant with principles and techniques of inferential statistics as applied in medical research and also have an understanding and ability to critically review secondary publications such as systematic reviews, meta-analysis and guidelines.

It is important for a clinical radiologist; to not only evaluate the diagnostic benefit of a technology but to also evaluate the benefit to the patients in terms of clinical outcome, keeping in mind the radiation dose to the patient, where the use of imaging modality with ionizing radiation is concerned. With evidence based radiology, the radiologist will be able to ensure better clinical care for the patients.

The limitation to the practice of Evidence Based Radiology is the paucity of studies in radiology that follow the evidence based principle of practice, and traditionally radiologists by and large have not enhanced their critical appraisal skills and have not focussed on hypothesis driven research, but that is changing.

I have no doubt, that exciting times are ahead, as far as Evidence Based Radiology practice is concerned, because it will lead to appropriate and efficient use of resources by the radiologists to address the patient's need and meet patient's expectations that will result in better clinical outcomes.

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Imaging of Brain Neoplasms in Adults:

Introduction:

Tumors related to central nervous system (CNS) are very rare neoplasms compring of 1-2% of all malignancies [5]. A recent report on the cancer registry survey conducted by Indian Council for Medical Research on Glioma incidence in India revealed 5.8% in Mumbai, 6.7% in Bangalore, 3.5% in Chennai, 5.6% in Dibrugarh, and 28.2% in Trivandrum among males and 6.3% in Mumbai, 5.6% in Bangalore, 7.5% in Chennai, 0% in Dibrugarh, and 21.8% in Trivandrum among females[4].

Imaging plays an important role in the evaluation of brain neoplasms, in regards to assessment of location, extent and characterization of intracranial tumors, and its post treatment follow up. There is no systemic staging, as primary brain tumors rarely spread outside the central nervous system. The following are clinical settings, in which imaging for brain neoplasm (**particularly gliomas**) is done**:**

a) Initial diagnostic workup**, b)** Imaging for surgical planning and or navigation and **c)** For follow up**.**

The initial imaging modality is largely dependent on availability, because of the varied clinical presentation of brain neoplasms. When initial imaging [Computed Tomography (CT) or Magnetic Resonance Imaging (MRI)] identifies an intracranial tumor, the imaging protocol used, should be designed, to extract as much information as is necessary to define the location, extent and characterization of the lesion. CT has an advantage over MRI in delineation of changes in the bony structures that may be caused by tumor, it can detect calcification in tumors, typically seen in oligodendrogliomas, and it detects hyperacute hemorrhage. All other phases of hemorrhage (except hyperacute) are seen on MR imaging. On CT scans, gliomas are hypo-attenuating and show varied enhancement pattern depending on the grade (pathologic) of the lesion.

When an initial non contrast imaging demonstrates an intra-axial or extra-axial space-occupying lesion, the use of intravenous contrast medium is mandatory for defining the extent and characterization of the intracranial space occupying lesion. The imaging modality of choice is Magnetic Resonance Imaging, but it is contraindicated in patients with cardiac pacemakers, aneurysm clips, cochlear implants and intraorbital metallic foreign bodies. Biopsy confirmation of suspected primary Central Nervous System (CNS) tumor is critical, either by needle biopsy prior to surgery, or at the time of surgical resection, except

when the lesion appears benign clinically and on imaging.

*The WHO classification of brain tumors is the basis for assessing prognosis and guiding therapy. The WHO grading of CNS tumors is based on the histologic features of the tumor [1, 2, 3].

The histologic grades are as follows:

WHO grade I includes lesions with low proliferative potential, a frequently discrete nature, and the possibility of cure following surgical resection alone.

WHO grade II includes lesions that are infiltrating and low in mitotic activity, but recur more frequently than grade I malignant tumors after local therapy. Some tumor types tend to progress to higher grades of malignancy.

WHO grade III includes lesions with histologic evidence of malignancy, including nuclear atypia and increased mitotic activity. These lesions have anaplastic histology and infiltrative capacity. They are usually treated with aggressive adjuvant therapy.

WHO grade IV includes lesions that are mitotically active, necrosis-prone, and generally associated with rapid preoperative and postoperative progression and fatal outcomes. The lesions are usually treated with aggressive adjuvant therapy.

* Adult Brain Tumors Treatment (PDQ) -WHO Classification of Adult Brain Tumors. May 14, 2013. NIH. National Cancer Institute. Available athttp://www.cancer.gov/cancertopics/pdq/treatment/adultbrain/Health Professional/page 2. Accessed December, 9, 2013.

The term malignant gliomas comprises of glioblastoma, anaplastic astrocytoma, anaplastic oligodendroglioma and mixed anaplastic astrocytoma. The first is WHO grade IV, while the rest WHO grade III.

Initial dignostic workup

MRI is a modality of choice for detection of brain neoplasms, because of its excellent soft tissue contrast and resolution and it also provides functional information. Morphologic MR imaging is performed using pre contrast sagittal T1W, axial T1W, T2W, FLAIR, T2*GRE and coronal T2W sequences followed by post contrast T1W sequences in three (axial, coronal and sagittal) planes. Most of the information that is needed is seen on Morphologic MR imaging and it is still the basis for diagnosis and grading. Morphologic MR imaging relies on the location and size of the lesion, disruption of blood brain barrier and patient demographics to arrive at a probable differential diagnosis, however disruption of blood brain barrier is not a reliable differentiator between high grade and low grade tumors, as approximately 25 -30 per cent of non-enhancing gliomas are malignant,and approximately 25% low grade gliomas show enhancement.

Advanced MR imaging techniques (Physiology-based) like Diffusion Weighted Imaging (DWI), MR Spectroscopy (MRS) and MR Perfusion scans improve sensitivity and specificity of tumor diagnosis.

Diffusion weighted imaging (DWI) through characterization of water mobility in tissues assesses,

tissue microstructure. Commonly used b-value for DWI of brain is 1000. There is inverse correlation between DWI and cellular density. Clinical applications of DWI in brain tumor imaging are assessing tumor grade and cellularity, peritumoral edema, integrity of white matter tracts and post op status. DWI targets cellularity for quantitative assessment, lesions with high cellularity show restricted diffusion, which is quantifiable as low values of Apparent Diffusion Coefficient (ADC), these low ADC values when seen in solid brain neoplasms indicate higher grade, but coexistent edema can make reliable separation between high and low grade gliomas difficult. The range of ADC values with any brain tumor varies markedly; attesting to the fact of tumor heterogeneity. DWI can differentiate between cytotoxic and vasogenic edema. Primary CNS lymphomas show restricted diffusion due to high cellularity. Restricted diffusion in post op setting could represent surgical injury and/or devascularization injury and is not always tumor, this knowledge helps in follow up imaging. DWI can differentiate between necrotic peripherally enhancing tumor and pyogenic abscess. Pyogenic abscess shows high signal intensity on DW images, not usually seen in tumors, except occasionally, when biopsy of such lesions is inevitable.

Proton magnetic resonance spectroscopy MR Spectroscopy (Single Voxel Spectroscopy/ Multivoxel Spectroscopy) of the brain provides an in vivo noninvasive assessment of the chemical environment in regions of interest in the brain and insight into tumor characteristics, it assesses tumor metabolism. The tumor

spectral data should always be compared to contralateral healthy tissue, wherever and whenever possible. Multivoxel spectroscopy technique is also known as Magnetic Resonance Spectroscopic Imaging (MRSI) or Chemical shift imaging.

The proton (H) MR spectrum comprises a set of peaks distributed along x-axis, displaying the chemical of the metabolites labelled in units of parts per million (ppm). The ppm increases from right to left. The amplitude of resonances is measured along y-axis (an arbitrary scale). Three prominent peaks are consistently seen. **N-acetyl aspartate (NAA)** and other N-acetyl containing compounds at 2.02, a brain specific molecule is a reliable marker for monitoring neuronal impairment and dysfunction; **Creatine**, its concentration is relatively constant across the brain with very little variation in differing pathologies and is typically used as an internal standard, for calculating metabolite ratios, however caution is advised when doing so, it is seen at 3.02; and **Choline** represents soluble constituents of cell membrane, elevation of choline peak is related to alterations in membrane turnover and hence its increase is seen in conditions such as malignancy (all neoplastic lesions) and demyelination where there is rise in cell proliferation or membrane disruption, it is seen at 3.2. Elevated choline is reflected as increase in choline/NAA and choline/creatine ratios.

The other metabolites that are seen include Myoinositol at 3.56 ppm (its increase is thought to represent glial proliferation) and Glutamine and Glutamate are seen

at 2.12 and 2.35 and 3.74 and 3.75 ppm respectively, when spectra are obtained with short echo times. Elevated Myoinositol is seen in low grade neoplasms.

Lactate is a doublet peak seen at 1.33 ppm; it is more conspicuous when short echo-times (20-40ms) or long echo-times (270-288ms) are used to obtain spectra, the reliable way to differentiate it from overlapping lipid signal is to obtain spectra at intermediate echo-times (135-144ms), which inverts the lactate doublet peak below baseline, lactate indicates anaerobic glycolysis by tumor tissue.

Lipids (long chain fatty acids) are broad and are located between 0.9ppm and 1.3ppm, elevated lipid levels are seen within high grade brain tumors and metastases, representing areas of necrosis or hypoxia.

It is important to differentiate between high grade and low grade brain tumors as it has prognostic implications; brain tumors in general show elevation of choline and lactate and lipids with reduction in NAA. For grading of tumors; lipids and lactate indicate a higher grade and so does elevated choline, however elevated choline lacks specificity, as it is elevated in pilocytic astrocytomas and oligodendrogliomas and increased choline may be seen in infarctions (gliosis or ischemic damage to myelin or inflammation (glial proliferation). The threshold value of choline/creatine ratio used for differentiating between high grade and low grade gliomas is either 2.0 or 2.5.

MRSI can differentiate glioblastoma from metastasis as there are elevated metabolite concentrations (elevated

choline/creatine ratio) in perilesional tissues in glioblastoma, white absence of NAA in an intra-axial lesion is suggestive of its origin outside the central nervous system or a very malignant tumor that has destroyed all neurons at the site of the lesion. Infiltrating brain tumors can also be detected by MRSI, they show decreased NAA and elevated choline and Choline/NAA ratio. It is possible to differentiate between an abscess and necrotic peripherally enhancing neoplasm using MRSI, by placing a volume of interest in the enhancing area, presence of elevated choline favors a neoplasm.

When post irradiation patients are evaluated, choline/creatine ratio and/or choline/NAA ratios are higher in recurrent tumor as compared to radiation injury. MRSI can be used, to guide stereotactic biopsy of brain tumors as these tumors are heterogeneous.

MR Perfusion: Perfusion weighted imaging is performed using tracking of a contrast bolus with a dynamic MR sequence sensitive to T2* effects. The relative cerebral blood volume (**rCBV**) is a widely used quantitative variable derived from dynamic contrast enhanced MR imaging. The area under the curve so generated, is representative of rCBV, it must be remembered that extravasation of contrast due to disruption of blood brain barrier affects calculation of rCBV and needs to adjusted with a mathematical model or the application of a preloading dose of contrast to minimize this effect.The rCBV in high grade gliomas is increased as high grade gliomas develop increased macro and microvasculature, and this correlates with aggressive tumor growth. In astrocytoma; a subtype

of gliomas, vascular morphology determines malignant potential and survival. However it must be remembered that non-astrocytic low grade gliomas (like Oligodendrogliomas) have high rCBV. Primary CNS lymphomas show elevated rCBV but not as high as in glioblastomas.

These advanced MR imaging techniques are complementary to morphologic MR imaging, they add sensitivity and increase specificity in the initial diagnostic work up and are invaluable tools for follow-up imaging.

Imaging for surgical planning and navigation

The imaging protocol for surgical navigation depends on the navigation equipment, contrast administration is essential, and a dedicated 3D T1-weighted FSPGR sequence with fiducial markers is necessary and the ability to export the acquired images to the navigation equipment. When planning stereotactic biopsies, a frame-based technique requiring a CT scan or with an MR compatible stereotactic frame, an MRI scan should be performed.

Functional MR imaging using **BOLD** (**B**lood-**O**xygen-**L**evel-**D**ependent) sequence should be performed to delineate eloquent areas, their spatial relationship and proximity to the tumor, to plan surgical approach and extent of resection, thereby reducing risk of collateral damage, as BOLD fMRI directly visualizes functional area of brain adjacent to tumor. The results of fMRI can alter neurosurgical approach or guide the neurosurgeon away from, when the risk of damage to

eloquent area is high. The limitation of BOLD fMRI is that information is limited to the cortex; it cannot evaluate adjacent white matter.

Diffusion Tensor Imaging (DTI): It is different from DWI because of its sensitivity to anisotropy (i.e directionally dependent diffusion). It provides information on 3D diffusivity. It delineates integrity of white matter tracts and their spatial relationship to the tumor, is important in surgical planning and the decision to operate or not depends on accurate localization of white matter tracts. Diffusion tractography is an application of DTI that uses diffusion tensor data to identify specific white matter tract, this ability to identify specific fiber tracts impacts the way brain tumors are treated.

Follow-up imaging

MRI is an ideal modality for follow up imaging (one of sequence should be a 3D sequence to allow for assessment of post resection residual tumor volume), to assess response, to distinguish response from pseudo-response and also to distinguish tumor progression from pseudo-progression.

Post operative baseline MRI scan pre and post contrast (Gadolinium) should be performed preferably within 24 to 48 hours but not later than 72 hours after surgery to document the extent of resection (**level of evidence 3, Recommendation grade B**) and to avoid misinterpreting post-operative changes as residual disease because complete resection of bulky tumors is associated with improved overall survival in both

high grade and low grade gliomas, complete resection in low grade gliomas involves complete resection of T2 /FLAIR hyperintensity and persistence of T2/FLAIR hyperintensity after recovery period (upto 12 weeks, to allow for resolution of edema) is interpreted as residual disease. It must be noted that there could be an element of postoperative ischemia/ infarction in postoperative imaging, which must be documented with DWI (within 72 hours after surgery); it would show up as an area of restricted diffusion. Comprehensive follow up imaging should include both morphologic as well as physiology based MR imaging.

In post irradiation setting, Single Photon Emission Computed Tomography (SPECT) and Positron Emission Tomography (PET) may be useful in differentiating tumor recurrence from radiation necrosis

Response assessment

The changes in the bi dimensional measurements of enhancing lesions are basis for response assessment to therapy in both **Macdonald and RANO** (Response Assessment in Neuro-Oncology) **Criteria.** The **RANO** criteria that assessed one of the deficiencies of Macdonald criteria, was the lack of evaluation of non enhancing area, but it does so qualitatively. The areas of increased T2 and FLAIR signal and mass effect are considered as non enhancing tumor, but there is no reliable way differentiating it from edema and/or gliosis. The RANO criteria consider changes in T2 and FLAIR hyperintensity as potential non enhancing tumor, but not assess these changes quantitatively and in the era

of antiangiogenic therapy, relying on change in contrast enhancement (decrease) could result in misinterpretation as tumor response. The use of steroids also alter contrast enhancement. Physiology based MR imaging is being explored in trial settings and could provide answers in the future.

On imaging, response assessment of contrast enhancing (target) lesions is as per following criteria:

Complete Response (**CR**) is defined as disappearance of all target lesions (pseudo-response needs to be excluded); Partial Response (**PR**) is defined as a decrease in Sum of Products diameters [two maximal diameters perpendicular to each other in same image, cavity, cyst and necrotic area are not included] (**SPD**) of >/= 50 per cent of base line value (pseudo-response needs to be excluded); Stable Disease (**SD**) is defined as less than 50 per cent decrease in SPD or less than 25 per cent increase in SPD, and Progressive disease (**PD**) is defined as increase in SPD of more than 25 per cent or increase in SPD of more than 25 per cent from nadir value (pseudo progression needs to excluded). Occasionally technical factors preclude assessment of tumors and should be recorded as Unable to Assess. **CR** and **PR** need to confirmed after 4 weeks

Response assessment criteria for T2/FLAIR hyperintense lesions

Improvement is defined as a decrease in signal abnormality, **Unchanged** is defined when there is no change as compared to previous imaging, **Worse** is

defined as unequivocal worsening or progression of signal abnormality (could also be a result of radiation effects, infarction or demyelination) and **Unable to Assess** (UA) when technical factors preclude assessment.

The following is a definition of **Pseudo-response**: Looks like response, occurs within 4 weeks of antiangiogenic drug therapy, needs to confirmed after at least 4 weeks after prior imaging.

The following are criteria for **Pseudo-progression**: Enhancement that simulates tumor growth, caused by radiation, growth of existing lesions or appearance of new lesion with 12 weeks of completion of radiation therapy, continued follow-up imaging can resolve issues, if the lesion continues to enlarge, the initial growth is labeled as true progression and if the lesion shrinks or stabilizes, the initial growth is labeled as pseudo-progression. In these cases the baseline SPD is not used when choosing nadir value for determining the time of progression. DWI can help in distinguishing between pseudo-progression and true progression. MR perfusion and MRSI are being explored in trial settings.These are the challenges faced in radiographic evaluation, in follow-up imaging.

The imaging changes always should be interpreted with due attention to the clinical context.

Conclusion

MR imaging is the mainstay of brain tumor assessment, whether for initial diagnostic work-up, surgical

planning / navigation or follow-up. MR imaging has transitioned from morphologic MR imaging to physiology based MR imaging, these are complementary techniques that are and should be a part of standard brain tumor imaging protocol, the results of these complimentary techniques provide meaningful clinical endpoints and imaging biomarkers for clinical trials and play an essential role in the day to day assessment of brain tumors.

Evidence for Neuroimaging [6]*

Brain imaging is necessary for optimal localization, characterization and management of brain cancer patients prior to surgery in patients with suspected or confirmed brain tumors (strong evidence)

Due to its superior soft tissue contrast, direct multiplanar capability and biosafety Magnetic Resonance imaging (MRI) with and without gadolinium based intravenous contrast is preferred method for brain cancer imaging, when compared to computed tomography (moderate evidence)

No adequate data exists on the role of imaging in monitoring brain cancer response to therapy and differentiating between tumor recurrence and therapy related changes (insufficient evidence)

No adequate data exists on role of non-anatomic physiology based imaging such as proton MR spectroscopy, DW-MRI and Perfusion MRI, and nuclear imaging (SPECT and PET) in monitoring treatment response or predicting prognosis and outcome in patients with brain cancer (insufficient evidence)

Human studies conducted on the use of MR spectroscopy brain tumors demonstrate that this noninvasive method is technically feasible and suggest potential benefits for some of the proposed indications. However there is paucity of high quality direct evidence demonstrating the impact on diagnostic thinking and therapeutic decision making.

There is added value of fMRI in surgical planning of patients with suspected brain cancer or focal brain lesions (moderate evidence) ***Ref: S Cha Department of radiology and Biomedical Imaging UCSF Medical Center California.**

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Imaging in Head & Neck Cancer

Head and neck cancer usually refers to squamous cell cancer (SCC) of the upper aero digestive tract that comprises primarily of a) oral & pharyngeal cancers and b) laryngeal cancers.

Why imaging?

The multidimensional role of imaging in the evaluation of head & neck cancers is—

- Accurate staging (as clinical examination is unable to assess the deep extent of disease)
- Assessing therapeutic options (surgery, chemotherapy or radiotherapy, single modality or multimodality)
- To guide biopsies
- To evaluate treatment response
- Post treatment surveillance - distinguishing post treatment changes from recurrence

Imaging Methods

The imaging methods that have a role in the evaluation of head & neck cancers are *contrast enhanced CT, contrast enhanced MRI, Ultrasonography* and *PETCT scanning*. Multidetector CT (MDCT) scanners have widely replaced conventional and helical CT scanners. 16 or higher section MDCT scanners provide high resolution isotropic reformations with clarity.

In general MRI is preferred in the suprahyoid neck and CT is preferred in the infrahyoid neck.

MRI is superior for evaluating skull base marrow invasion, perineural spread , dural invasion, cavernous sinus invasion and retropharyngeal adenopathy. In the oral cavity, the tumor –tongue contrast is best studied on contrast enhanced MRI. Posterior extent and proximity to hyoid is well seen on sagittal T1 post gadolinium and T2W MRI sequences. Involvement of prevertebral fascia in pharyngeal malignancies is best ruled out when the sagittal non-contrast T1W MR sequence shows a preserved fat stripe. The superior soft tissue characterization helps differentiate benign and malignant salivary gland neoplasms, differentiate post treatment changes from recurrence and differentiate secretions in the paranasal sinuses from tumor.

Contrast enhanced MDCT is preferred however in gingival, buccal and retromolar trigone malignancies. This is because the incidence of bone erosion in these varies from 12%-56% and CT has the highest specificity for bone erosion. Bone and soft tissue algorithms with multiplanar reformations are essential. MRI is known

to overestimate mandibular cortical erosion due to chemical shift artifacts as well as overestimate the inferior alveolar canal invasion. In the infrahyoid neck, the faster speed of scanning is a great advantage with CT in imaging the larynx and hypopharynx. Bone algorithms (not bone windows alone) are needed to evaluate the laryngeal cartilages.

Ultrasonography (US) has a role in evaluating superficial structures such as the thyroid, neck nodes and salivary glands. US is the first line investigation for a suspected thyroid nodule in a euthyroid/ hypothyroid gland. It can identify abnormal cervical nodes and is useful for guiding real time fine needle aspiration (FNA).

The role of PETCT in the pretreatment staging of head neck cancers is for evaluating distant metastases in those with stage III or IV cancers and to map the extent of neck node disease prior to radiation therapy planning. It is also useful for evaluating an unknown primary with neck node metastases and can detect upto 27% of primaries. PET CT has an important role in post treatment assesment of response, optimally at ≥ 12 weeks; a meta analysis has reported a high negative predictive value of 95% to rule out viable disease. Further survellance with PET CT at follow up of 12 months is of limited benefit if the 3 month PET CT was negative.

Information from Imaging

Familiarity with the T staging of cancers in various head neck regions helps the radiologist provide a complete report to the clinician.

The important issues to be addressed while reporting head and neck cancers in various regions are:

I. Extent of Primary

A. Oral tongue & Floor of Mouth (FOM) SCC

- Tumor size and thickness*
- Involvement of extrinsic muscles (genioglossus, hyoglossus, palatoglossus, and styloglossus àstage T4a) and muscles of FOM.
- Extent upto or across midline; involvement of ipsilateral and contralateral vascular bundles.
- Posterior extent to base tongue, tonsil, rest of oropharynx, preepiglottic space and distance from hyoid bone.
- Mandibular involvement (stage T4a) and extent (middle third or lateral segment, lingual or both cortices).
- Posterior extent to masticator space and pterygoid plates (stage T4b)

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* Tumor thickness (TT) implies the deepest invasion of tumor from the mucosal surface; a > 4mm thickness on histopathology in tongue squamous cell cancers has been associated with higher incidence of neck node metastases and elective neck dissection being recommended in such cases. Imaging measurements of TT have correlated well with histopathology as per reports in literature. The measurement of TT depends on the epicenter of the tumor; it is a lateral to medial dimension in tumors with epicenter along the lateral border and a superior to inferior dimension in tumors arising along the ventral surface. Contrast enhanced T1W MRI is the sequence with the highest accuracy for TT measurement.

B. Gingival, buccal and Retromolar tigone (RMT) SCC

- Tumor size
- Mandibular erosion (stage T4a) and extent (AP & height) –axial, coronal & oblique reformations help assessing this**
- Extension to maxillary sinus or skin of face (stage T4a); and to premaxillary region upto the zygoma.
- Extension to lingual muscles, base tongue and FOM (stage T4a)
- Extension to pterygopalatine fossa, pterygoid plates and encasement of carotid arteries (T4b).

** The coronal and oblique reformation in bone and soft tissue algorithm are very useful for studying the alveolar crest and recording depth of erosion. The reformations, particularly the oblique reformat are best generated ad hoc and studied interactively on the work station using triangulation. *Optional information*—If no erosion is present and a large para-mandibular soft tissue mass is noted, the height of the mandibular shaft (from the lower border) that is free of contact with the tumor is useful to record. If more than 1cm height of the mandibular shaft from the lower border is free of contact with the tumor (in a dentate nonirradiated mandible) that includes the region above the inferior alveolar canal, a marginal mandibulectomy could be offered.

- Masticator space (T4b) –specify muscle involved (medial or lateral pterygoid); and in case of masseter or temporalis invasion, extension above or below mandibular sigmoid notch#.

#- Posterior soft tissue spread to masticator space is no longer "unresectable" and a subset below the mandibular (sigmoid) notch involving the medial pterygoid is resected by most surgeons. Disease extending above the sigmoid notch is not offered resection at our institute as literature reports poor local control and overall survival in this group. Examine the axial images. The notch is seen approximately at one level below where the vertical ramus divides into the coronoid and condyloid process. Recording disease spread above this level or below this level is useful information to the surgeon.

C. Oropharyngeal SCC

- Tumor size
- Involvement of subsites—base tongue, tonsil, soft palate, posterior pharyngeal wall
- Invasion of hard palate, mandible, extrinsic tongue muscles (T4a)
- Invasion of medial pterygoid muscle; of larynx (T4a)
- Invasion of lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, skull base and carotid artery (T4b)
- Involvement of prevertebral fascia

D. Nasopharyngeal SCC

- Involvement of subsites –lateral wall, posterior wall, roof
- Spread to parapharyngeal space, (T2) retropharyngeal space, prevertebral fascia
- Spread to skull base & paranasal sinuses (T3)
- Spread to masticator space & carotid sheath (T4)
- Perineural spread and cavernous sinus invasion (T4)
- Spread to orbits (T4)

E. Laryngeal SCC

- Supraglottis/ glottis/ subglottis OR Transglottic
- Tongue base and valleculae (for supraglottic/ transglottic cancers)
- Extension to preepiglottic or paraglottic space (T3)
- Anterior and posterior commissure
- Hyoid bone—intact/ eroded
- Thyroid cartilage— Erosion of inner cortex (T3) / outer cortex (T4a) ; sclerosis present or not
- Exolaryngeal spread – to strap muscles, esophagus, thyroid gland, trachea, or extrinsic muscles of the tongue (T4a)
- Cricoid & arytenoid cartilage lysis/ sclerosis

- Pyriform sinuses, PC region, posterior pharyngeal wall
- Prevertebral fascia (stage T4b)
- Carotid sheath (stage T4b)
- Mediastinum (stage T4b)

F. Hypopharyngeal SCC

- Pyriform sinuses, PC region, posterior pharyngeal wall
- Aryepiglottic fold, valleculae, false and true cords
- Epiglottis and pre-epiglottic space
- Paraglottic space (T3)
- Thyroid cartilage— Erosion of inner cortex (T3) / outer cortex (T4a) ; sclerosis present or not
- Exolaryngeal spread – to strap muscles, esophagus, thyroid gland, trachea, or extrinsic muscles of the tongue (T4a)
- Cricoid & arytenoid cartilage lysis/ sclerosis
- Prevertebral fascia(stage T4b)
- Carotid sheath (stage T4b)
- Mediastinum (stage T4b)

II. Nodes

Tips— Examine the draining region with greater suspicion; look for necrosis, heterogeneity, irregular margins, increased enhancement, rounded shape in that order. In lesions approaching/crossing midline, examine the contralateral neck as well.

Check list for reporting—

- Number & size of largest abnormal node at each level (using AJCC level based neck node classification).
- Presence of necrosis/extracapsular spread (seen as illdefined margins)
- Invasion of adjacent structures and vessels. Invasion of carotid arteries is particularly important and can be discerned by measuring the circumferential contact (cc) with the node (if cc $\geq 270^{o}$, the artery is invaded; if $\leq 180^{o}$, it is easily resectable) .

Important questions in Head & Neck Cancers

1. What is the best method for assessing mandibular invasion in Oral Cancers?

Mandibular invasion in oral cancers influences management that can vary from the conservative marginal mandibulectomy (which preserves function and cosmesis) to the more extensive segmental mandibulectomy. Marginal mandibulectomy that preserves cosmesis and function, involves rim resection of the mandible and is practiced when a) erosion is subtle or b) when disease abuts the mandible, yet no erosion is seen (for oncologically safe resection margins). It can be achieved when an at least 1.0cm height of the shaft of the mandible can be preserved (to prevent fracture). Segmental mandibulectomy is performed when a) there is significant cortical erosion with invasion of the marrow b) in edentulous and

irradiated mandibles or c) when a bulky soft tissue component of oral squamous cancer abuts a large surface area of the mandible even without erosion (in order to obtain tumor free resection margins). Hemimandibulectomy is offered when the inferior alveolar canal and mandibular foramen are invaded.

Clinical examination alone is insufficient to predict bone invasion. Mandibular invasion has been extensively evaluated by various imaging methods such as Orthopantomography (OPG), bone scan, conventional CT, Denta scan, single photon emission computed tomography (SPECT), PETCT, MRI, multidetector CT (MDCT) and Cone beam CT. The quest has been to identify a modality with the highest sensitivity for detecting invasion without reducing specificity.

OPG has a reported low specificity for mandibular erosion due to periodontitis and odontogenic infections , particularly in tobacco chewing populations. Detection of erosion requires at least 30% mineral loss and midline erosions can be missed. SPECT has the highest sensitivity of 100% for mandibular invasion, but very low specificity (29%). Bone scanning has lower sensitivity as well as specificity. Dentascan, a CT software originally designed to evaluate dental implants, has a reported sensitivity of 95% and specificity of 79% for mandibular invasion. Conventional CT with 3mm sections in bone and soft tissue algorithms was reported to have high specificity (87%) and high sensitivity (96%) for mandibular invasion in OCSCC. The PET component of PET/CT images does not add to CT information for identification

of bone infiltration. Comparison of MRI with CT by Imaizumi et al revealed that MRI overestimated cortical erosion as well as inferior alveolar canal involvement. Multidetector CT has been investigated in few studies and has revealed high sensitivity and specificity for mandibular invasion. Using 16 or higher section MDCT with thin sections and multiplanar reformations along with bone and soft tissue algorithms can exploit the full potential of MDCT. Viewing on a workstation or volume viewer with triangulation after generating ad hoc reformats is preferred to technologist generated reformations. Using this we recently reported 94 % sensitivity and 90% specificity for assessing mandibular invasion in RMT SCC.

Conclusion—MDCT is the best single modality with highest specificity and positive predictive value for mandibular invasion in oral squamous cancers. It has high sensitivity.

2. What is the current role of imaging in evaluating neck node metastases?

Cervical nodal metastasis is an important prognostic factor, a single ipsilateral node reducing survival by 50 % and a single contralateral node reducing survival to 33%. When metastatic nodes are detected on clinical examination and confirmed with imaging, it is referred to as the N_+ neck (N_1- N_3 of AJCC stage). When nodal metastases are absent on clinical examination, it is called a clinically negative (N0) neck. Imaging is required to map the nodal disease in the N+ neck and detect and map occult metastasis in the N0 neck.

SCC from each site has a specific drainage area/s for lymph nodes that need to be examined with greater care before declaring it as N0 on imaging. Tongue cancers usually spread to ipislateral level I and II nodes, but skip metastases to levels III and IV and contralateral metastases are known. Midline FOM SCC or tongue cancers reaching midline can spread to bilateral level II nodes. Nodal metastases from gingival, buccal and RMT SCC are usually to level IA, IB and II regions. Hard palate SCC is less frequently associated with adenopathy. Nasopharyngeal cancers spread to bilateral level II, level V, parotid and retropharyngeal nodes. Oropharyngeal cancers spread to level II and retropharyngeal nodes. Supraglottic laryngeal SCC spread to level II nodes while glottis, subglottis and hypopharyngeal cancers spread to level III and IV nodes. Isolated left supraclavicular nodes on the other hand are more likely to be from an abdominal or thoracic primary.

CT and MRI have similar accuracy for evaluating neck nodes and extranodal spread; necrosis is the most important feature indicative of metastasis. Size criteria in practice have limited value in detecting metastatic nodes, particularly in populations with increased incidence of tuberculosis and poor oral hygiene. The other features suggestive of metastasis are internal heterogeneity, rounded shape with loss of hilum and restricted diffusion with low ADC values on ADC maps.

Other imaging methods used for evaluating the neck have been US, US guided fine needle aspiration cytology (US g FNAC), contrast enhanced US, Diffusion

weighted MRI (DW MRI), dynamic contrast enhanced MRI (DCE MRI) and PETCT. US features of abnormal nodes are necrosis, abnormal internal echotexture, eccentric hypertrophy with dark hypoechogenicity, absent hilum and rounded shape either singly or in combination.

There are at least 4 meta-analyses that have compared the various imaging methods for detecting neck node metastases in head and neck cancers. The debondt et al meta-analysis compared US guided fine needle aspiration cytology (US g FNAC) with US, CT, MRI and Ultra small particle iron oxide MRI (USPIO MRI) and reported US g FNAC with the highest diagnostic odds ratio for detecting metastatic neck nodes with decreasing performance for US alone, USPIO MRI, CT and MRI in that order. A point to note is that this meta-analysis had 3 studies of USgFNAC, in which only one study was in the clinically negative neck, where the sensitivity of USgFNAC was as low as 48%.

Another meta-analysis by Wu et al studied the performance of MRI for nodal staging and compared it with other modalities. The reported sensitivity and specificity of MRI (76% and 86% respectively) was comparable with PET, CT and US. More important however is the role of imaging in the N0 neck to detect occult metastases. A third meta-analysis by Kyaz et al evaluating PET-CT in head and neck SCC reported that PETCT did not detect disease in half the patients with N0 neck. The latest meta-analysis by Liao et al in the N0 neck concludes that US, PET, CT& MRI have similar diagnostic accuracy to detect nodal metastases.

The pooled sensitivity and specificity of CT, MRI, PET and US were 52% & 93%; 65% & 81%; 66% & 87%; and 66% & 78% respectively. Currently however no imaging modality offers accuracy that can uniformly replace surgical staging of the neck. Sentinel node biopsy (SNB) is experimental, but has promising early results. A diagnostic meta-analysis of SNB in 847 patients of clinical T1/T2 N0 oral cavity and oropharyngeal SCC patients revealed an overall sensitivity of 93%.

Conclusion- CT, MRI, US and PETCT have comparable accuracy for evaluating neck node metastases, but are inferior to surgical staging.

3. What is the accuracy of imaging for laryngeal cartilage invasion?

Cartilage invasion is important information that impacts treatment of laryngeal cancers. The 7th edition AJCC TNM staging of laryngeal cancers for all subsites classifies invasion of inner cortex of thyroid lamina as T3; these can be treated with laryngeal conservation therapy with chemo-irradiation. Destruction of the entire thyroid cartilage (and/or cricoid cartilage in the subglottis) and/or extralaryngeal spread to surrounding soft tissues constitutes T4a. These cases are offered total laryngectomy if the prevertebral fascia, carotid artery and mediastinal structures are not invaded. Imaging ideally needs to differentiate between T3 and T4a, ie minor cartilage erosion from major cortical destruction and/or extralaryngeal spread.

Cartilage involvement on CT has been studied extensively. Thyroid cartilage is the most difficult to

evaluate due to patchy ossification. Becker et al evaluated multiple criteria for laryngeal cartilage involvement by SCC on CT. The most sensitive sign for cartilage invasion was *sclerosis*, but had a specificity of only 40%. When *erosion* or *lysis* was used as criteria, the specificity for all cartilages rose to 93%, but these were not sensitive criteria. The most specific sign was *extralaryngeal spread* (95%), but the sensitivity was as low as 44%. Using a combination of all features yields a sensitivity of 91% and negative predictive value of 95%.

Beitler et al using CT for assessing cartilage invasion reported a positive predictive value of 81% using extralaryngeal spread as criterion and 74% using erosion of both laryngeal cortices as criterion. Li et al evaluated MDCT for through and through invasion of thyroid cartilage and reported a PPV of 78%, with a NPV of 100%. Hence while a negative CT is highly accurate for absence of cartilage invasion, a positive CT result may result in overcalling cartilage invasion.

MRI has also been evaluated for cartilage invasion. Becker et al reassessed laryngeal cartilage invasion using revised criteria on MRI. The revised criteria help differentiate tumor from inflammatory changes. While tumor invaded cartilage is intermediate in signal intensity on T2W sequences (similar to adjacent tumor) with enhancement similar to tumor on postgadolinium images, the inflamed cartilage has much higher T2W signal intensity with enhancement higher than the tumor. An increase in specificity to 75% for cartilage invasion was reported using the revised criteria. MRI

has a higher sensitivity and NPV (95%), and hence has a problem-solving role after an equivocal CT.

Conclusion- CT is the usual method of evaluation of larynx and has a high negative predictive value if all features (sclerosis, lysis and extralaryngeal spread) are used. However the positive predictive value is low especially if sclerosis is used as criterion. In such cases MRI can be used a problem solving method due to its high negative predictive value.

Suggested reading

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Detection of cervical lymph node metastasis in head and neck cancer patients with clinically N0 neck-a meta-analysis comparing different imaging modalities.

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Abstract

Background:

How to properly manage clinically negative neck of head and neck cancer patients is a controversial topic. Research is now directed toward finding a method sensitive enough to bring the risk of occult metastases below 20%. The aim of this review was to compare the diagnostic accuracy of different imaging modalities, including CT, MRI, PET and US, in clinically N0 head and neck cancer patients.

Methods:

For this systematic review and meta-analysis, PubMed and the Cochrane Database were searched for relevant original articles published up to May 2011. Inclusion criteria were as follows: articles were reported in English; CT, MRI, PET or US were performed to identify cervical metastases in clinically N0 head and neck squamous cell carcinoma; and data were sufficient for the calculation of true-positive or false-negative values. A bivariate random effect model was used to obtain pooled sensitivity and specificity. The positive and negative test probability of neckmetastasis was generated based on Bayesian theory and collected data for different pre-test possibilities.

Results:

Of the 168 identified relevant articles, 7 studies fulfilled all inclusion criteria for CT, 6 studies for MRI, 11 studies for PET and 8 studies for US. There was no difference in sensitivity and specificity among these imaging modalities, except CT was superior to US in specificity.

The pooled estimates for sensitivity were 52% (95% confidence interval [CI], 39% ~ 65%), 65% (34 ~ 87%) 66% (47 ~ 80%), and 66% (45~77%), on a per-neckbasis for CT, MRI, PET and US, respectively. The pooled estimates for specificity were 93% (87% ~ 97%), 81% (64~ 91%), 87% (77~ 93%), and 78% (71~83%) for CT, MRI, PET and US, respectively. With pre-examination nodal metastasis probabilities set at 10%, 20% and 30%, the post-exam probabilities of positive nodal metastasis rates were 47%, 66% and 77% for CT; 27%, 46% and 59% for MRI; 36%, 56% and 69% for PET; and 25%, 42% and 56% for US, respectively. Negative nodal metastasis probabilities were 95%, 89% and 82% for CT; 95%, 90% and 84% for MRI; 96%, 91% and 86% for PET; and 95%, 90% and 84% for US, respectively.

Conclusions:

Modern imaging modalities offer similar diagnostic accuracy to define and diagnose clinically N0 neck. Minimizing morbidity and avoiding elective neck dissection is acceptable in some select cases.

Thyroid cancers

- Incidence of thyroid nodules is 20%-65% (on ultrasonography). Incidence of thyroid cancers is however <10%.
- 90% thyroid cancers are well differentiated (papillary and follicular cancers) with favorable prognosis; the rest are medullary or anaplastic cancers.
- TSH should be measured in all thyroid enlargement / any suspected nodule.

- If TSH is low, scintigraphy (^{99m}TcO4 /^{123}I / ^{131}I) is used for evaluation of nodule function.
- Scintigraphy is also used for detection/ ablation of residual disease after treatment.
- When TSH is high/ normal (hypothyroid or euthyroid) , *Ultrasonography (US) is the modality of choice* for confirming suspected thyroid nodule, detecting nodules and nodule characterization.
- CT/MRI have a role in evaluating disease extent in advanced disease; and in goiter with substernal extension.
- PETCT has a role in post treatment follow-up: a) In post total thyroidectomy status when thyroglobulin levels are rising and ^{131}I uptake is absent b) In post thyoidectomy status of high risk patients such as poorly differentiated thyroid cancers unlikely to concentrate ^{131}I, in Hurthle cell carcinoma & tall cell variants.

Ultrasonography

- By definition, a thyroid nodule is a discrete lesion within the thyroid gland that is radiologically distinct from the surrounding thyroid parenchyma.
- US thyroid is highly sensitive for detection of thyroid nodules, but less specific in characterizing into benign and malignant.
- US can however identify nodules with features suspicious for malignancy that can be needled real time under US guidance. The US features to decide guided fine needle aspiration (FNA) are discussed in table 1.

- If multiple nodules are seen on US, the nodule/s with suspicious features (table 1) to be needled; not the largest nodule.
- Subcm nodules do not merit FNA except those with microcalcification and those with high risk history (see foot note in table 1).
- US-guided FNA preferred with 25-26 G needle; on site cytology exam under light microscopy increases yield.
- US examination of the thyroid incomplete without evaluation of cervical nodes. Metastasis frequently occurs to central compartment (level VI including pretracheal) and lateral compartment (level III & IV). Both sides of neck need evaluation (as contralateral metastasis although less frequent is known). An abnormal node needs FNA.
- Metastatic nodes could be solid heterogeneous; solid with microcalcification (highly specific); solid-cystic or even purely cystic in papillary cancers (although primary may be solid).
- The role of preoperative US prior to thyroidectomy in proven thyroid cancer is for the status of the contralateral lobe and for both sided cervical nodes.
- Extracapsular spread with adjacent deep structure invasion/mediastinal extension requires further staging with CT/ MRI.
- A diffuse heterogeneous gland without abnormal nodes probably represents thyroiditis and does not need FNA.

Table 1: Ultrasound features of thyroid nodule used to decide guided FNA* (adapted from American Thyroid Association guidelines 2009)

Features		Implication	FNA
Solid nodule	Micro-calcification	Most specific feature for malignancy	Yes if ≥ 1cm.
	Coarse calcification	Seen in multinodular goiter/medullary/ papillary cancers	Yes if ≥1.5cm.
		Ominous in solitary nodules	
	Iso-hyperechoic	Follicular neoplasm	Yes if ≥1.5cm.
	Darkly hypoechoic	Favors malignancy	Yes if ≥1cm.
	✓ Increased vascularity, ill-defined margins & taller than wide nodule are other ominous features ✓ Complete uniform hypoechoic halo specific for benignancy.		
*High risk history*** & small nodule with suspicious features		Suspect malignancy	Yes >5 mm
Purely cystic		Benign	No
Solid Cystic		Ominous if solid parts have suspicious features	Yes if ≥2.0cm.
Spongiform Nodule		Nodular hyperplasia (99.7 - 100% specificity for benignancy)	No

* The three most important features to decide need for thyroid FNA are 1) Microcalcification 2) darkly hypoechoic nodule (particularly with ill defined margins) and 3) Increased vascularity in the nodule

** History of thyroid cancer in one or more first degree relatives; history of external beam radiation as a child; exposure to ionizing radiation in childhood or adolescence; prior hemithyroidectomy with discovery of thyroid cancer, 18FDG avidity on PET scanning; calcitonin >100 pg=mL, multiple endocrine neoplasia; familial medullary thyroid cancer (FMTC).

Suggested Reading

Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ et al.

Revised American Thyroid Association management guidelines_for patients with thyroid nodules and differentiated thyroid cancer. American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer Thyroid. 2009;19(11):1167-214.

Screening for Breast Cancer

INTRODUCTION

The primary aim of any cancer screening programme is to reduce the all cause and disease-specific mortality in the population that is being screened. The conditions that should be satisfied are that the disease which is being screened for should be an important health problem in the given population, the risks, both physical and psychological, from the screening should be less than the benefits and the costs should be balanced against the benefits. In the following discussion we will evaluate the current status of role of imaging based screening in breast cancer.

Role of Mammography

Screening reduces breast cancer mortality by 15% (irrespective of age at which screening is started) and over-diagnosis and overtreatment is at 30%.[1] This means that for every 2000 women invited for screening throughout 10 years, one will avoid dying of breast cancer and 10 healthy women, who would not have

been diagnosed if there had not been screening, will be treated unnecessarily.[1] Further more, more than 200 women will experience important psychological distress including anxiety and uncertainty for years because of false positive findings.[1]

Screening after the age of 50 years (surrogate for menopause) causes more benefit than that at younger age. A meta-analysis by KerlikowskeK et al for determining the efficacy of screening mammography by age, number of mammographic views per screen, screening interval, and duration of follow-up concludes that screening mammography significantly reduces breast cancer mortality by 26% in women aged 50 to 74 years after 7 to 9 years of follow-up, regardless of screening interval or number of mammographic views per screen[2]. There is no reduction in breast cancer mortality in women aged 40 to 49 years after 7 to 9 years of follow-up[2].

Screening often fails to detect aggressive interval cancers and over-diagnoses indolent ones. The sensitivity of mammography in the diagnosis of breast cancer is variable and inversely proportional to the breast density[3,4]. Mammographic sensitivity may be as low as 30%- 48% in patients with dense breasts, with much higher interval cancer rates noted in dense breasts[4]. Further more, mammographically dense breast tissue is now considered a significant risk factor for the development of breast cancer.

With advances in treatment, it is now not difficult to achieve good cure rates in early stage breast cancer

{small palpable lump detected by patient (Breast self examination-BSE) or clinician (Clinician Breast Examination-CBE)}. Though not shown in a Randomized trial format, both BSE and CBE are likely to detect cancers in early curable stage (on-going study in Tata Memorial Centre).

The US and Canadian Preventive task force currently recommend screening starting at the age of 50 years. The ethnic background and the population pyramid of India (wider population below 50 years) are not comparable to that of the western world on which these results are based. Breast cancer is not the leading cause of death in a developing country like ours. Even more important is the fact that easy access to healthcare is not available to a large proportion of the population. Keeping this in background, a nation-wide mammography screening programme seems unjustified. Decision to undergo regular screening should be a well informed choice made by the clinician and the patient, depending up on the risk factors like family history, earlier biopsies showing high risk features like Atypical ductal or lobular hyperplasia, lobular carcinoma in situ, use of hormone replacement therapy, radiation to the chest wall in the past, obesity, nulliparity, etc.

Role of Ultrasonography

There is no role of ultrasound alone in screening for breast cancer. A combination of mammography and ultrasound for screening of breast cancer has shown increased detection rate(improved sensitivity) which

comes at a cost of unacceptable high false positives and increased biopsy rates. Adding a single screening ultrasound to mammography in women with elevated risk of breast cancer will yield an additional 1.1 to 7.2 cancers per 1000 high-risk women, but it will also substantially increase the number of false positives[5]. However there is no study (more likely because of logistics) that shows reduction in mortality due to incremental value of ultrasound to mammography. It at best can serve as an additional tool to mammography screening in women with intermediate and high risk for breast cancer (personal history of breast cancer or biopsies associated with increased risk or relative with early onset breast cancer).

Role of MRI

There is no role of MRI in screening of women at average or intermediate risk for breast cancer. There is no randomized controlled trial (RCT) showing reduction in mortality due to addition of MRI in screening of women with high risk as well. There are several prospective studies that show increased efficacy of MRI in detection of breast cancer as compared to mammography alone in this subset of women and hence performing a RCT in the light of these trials seems ethically unfeasible. The definition of high risk in these trials has been varying though most of the trials have focused on women with family history or genetic mutation. A Systematic Review of eleven such studies concludes that combined sensitivityof MRI and mammography is excellent, though not 100%, and is a

viable alternative to prophylactic mastectomies when combined with other risk reducing measures like chemoprevention or oopherectomies in very high risk women who are willing to accept some risk[6].

Conclusion:

There has to be a transfer of unbiased information between the clinician and the patient regarding the benefits and harms of screening. It cannot be recommended as a national programme for our country. It can be best used when tailored to the given patient at hand (Opportunistic Screening). For women at an average risk, BSE combined with CBE are likely to be beneficial. For women at intermediate risk and high risk, mammographic screening with addition of ultrasound may be recommended. For women with proven genetic mutation predisposing her to breast cancer, a combined screening with MRI and Mammography is suggested in addition to other forms of risk reducing measures.

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Background:

A variety of estimates of the benefits and harms of mammographic screening for breast cancer have been published and national policies vary.

Objectives:

To assess the effect of screening for breast cancer with mammography on mortality and morbidity.

Search strategy:

We searched PubMed (22 November 2012) and the World Health Organization's International Clinical Trials Registry Platform (22 November 2012).

Selection criteria:

Randomized trials comparing mammographic screening with no mammographic screening.

Data collection and analysis:

Two authors independently extracted data. Study authors were contacted for additional information.

Main results:

Eight eligible trials were identified. We excluded a trial because the randomization had failed to produce comparable groups. The eligible trials included 600,000 women in the analyses in the age range 39 to 74 years. Three trials with adequate randomization did not show a statistically significant reduction in breast cancer mortality at 13 years (relative risk (RR) 0.90, 95% confidence interval (CI) 0.79 to 1.02); four trials with suboptimal randomization showed a significant reduction in breast cancer mortality with an RR of 0.75 (95% CI 0.67 to 0.83). The RR for all seven trials combined was 0.81 (95% CI 0.74 to 0.87).

We found that breast cancer mortality was an unreliable outcome that was biased in favour of screening, mainly because of differential misclassification of cause of death. The trials with adequate randomization did not find an effect of screening on total cancer mortality, including breast cancer, after 10 years (RR 1.02, 95% CI 0.95 to 1.10) or on all-cause mortality after 13 years (RR 0.99, 95% CI 0.95 to 1.03).

Total numbers of lumpectomies and mastectomies were significantly larger in the screened groups (RR 1.31, 95% CI 1.22 to 1.42), as were number of mastectomies (RR 1.20, 95% CI 1.08 to 1.32). The use of radiotherapy was similarly increased whereas there was no difference in the use of chemotherapy (data available in only two trials).

Authors' conclusions:

If we assume that screening reduces breast cancer mortality by 15% and that overdiagnosis and overtreatment is at 30%, it means that for every 2000 women invited for screening throughout 10 years, one will avoid dying of breast cancer and 10 healthy women, who would not have been diagnosed if there had not been screening, will be treated unnecessarily. Furthermore, more than 200 women will experience important psychological distress including anxiety and uncertainty for years because of false positive findings. To help ensure that the women are fully informed before they decide whether or not to attend screening, we have written an evidence-based leaflet for lay people that is available in several languages on

www.cochrane.dk. Because of substantial advances in treatment and greater breast cancer awareness since the trials were carried out, it is likely that the absolute effect of screening today is smaller than in the trials. Recent observational studies show more overdiagnosis than in the trials and very little or no reduction in the incidence of advanced cancers with screening.

2. Kerlikowske K, Grady D, Rubin SM, Sandrock C, Ernster VL. Efficacy of screening mammography: a meta-analysis. JAMA 1995; 273:149-154

Objevtive:

To determine the efficacy of screening mammography by age, number of mammographic views per screen, screening interval, and duration of follow-up.

Design:

Literature review and meta-analysis.

Data identification and analysis:

Literature search of English-language studies reported from January 1966 to October 31, 1993, using MEDLINE, manual literature review, and consultation with experts. A total of 13 studies were selected, and their results were combined using meta-analytic techniques based on the assumption of fixed effects.

Main results:

The overall summary relative risk (RR) estimate for breast cancer mortality for women aged 50 to 74 years

undergoing screening mammography compared with those who did not was 0.74 (95% confidence interval [CI], 0.66 to 0.83). The magnitude of the benefit in this age group was similar regardless of number of mammographic views per screen, screening interval, or duration of follow-up. In contrast, none of the summary RR estimates for women aged 40 to 49 years was significantly less than 1.0, irrespective of screening intervention or duration of follow-up. The overall summary RR estimate in women aged 40 to 49 years was 0.93 (95% CI, 0.76 to 1.13); the summary RR estimate for those studies that used two-view mammography was 0.87 (95% CI, 0.68 to 1.12) compared with 1.02 (95% CI, 0.73 to 1.44) for those studies that used one-view mammography, and for those studies with 7 to 9 years of follow-up, the summary RR estimate was 1.02 (95% CI, 0.82 to 1.27) compared with 0.83 (95% CI, 0.65 to 1.06) for those studies with 10 to 12 years of follow-up.

Conclusion:

Screening mammography significantly reduces breast cancer mortality in women aged 50 to 74 years after 7 to 9 years of follow-up, regardless of screening interval or number of mammographic views per screen. There is no reduction in breast cancer mortality in women aged 40 to 49 years after 7 to 9 years of follow-up. Screening mammography may be effective in reducing breast cancer mortality in women aged 40 to 49 years after 10 to 12 years of follow-up, but the same benefit could probably be achieved by beginning screening at menopause or 50 years of age.

3. **Kolb TM, Lichy J, Newhouse JH: Comparison of the performance of screening mammography, physical examination, and breast US and evaluation of factors that influence them: An analysis of 27,825 patient evaluations. Radiology 225:165-175, 2002.**

Purpose:

To (a) determine the performance of screening mammography, ultrasonography (US), and physical examination (PE); (b) analyze the influence of age, hormonal status, and breast density; (c) compare the size and stage of tumors detected with each modality; and (d) determine which modality or combination of modalities optimize cancer detection.

Materials and methods:

A total of 11,130 asymptomatic women underwent 27,825 screening sessions, (mammography and subsequent PE). Women with dense breasts subsequently underwent screening US. Abnormalities were deemed positive if biopsy findings revealed malignancy and negative if findings from biopsy or all screening examinations were negative.

Results:

In 221 women, 246 cancers were found. Sensitivity, specificity, negative and positive predictive values, and accuracy of mammography were 77.6%, 98.8%, 99.8%, 35.8%, and 98.6%, respectively; those of PE, 27.6%, 99.4%, 99.4%, 28.9%, and 98.8%, respectively; and those of US, 75.3%, 96.8%, 99.7%, 20.5%, and 96.6%,

respectively. Screening breast US increased the number of women diagnosed with nonpalpable invasive cancers by 42% (30 of 71). Mammographic sensitivity declined significantly with increasing breast density (P <.01) (48% for the densest breasts) and in younger women with dense breasts (P =.02); the effects were independent. Mammography and US together had significantly higher sensitivity (97%) than did mammography and PE together (74%) (P <.001). Tumors detected at mammography and/or US were significantly smaller (P =.01) and of lower stage (P =.01) than those detected at PE.

Conclusion:

Mammographic sensitivity for breast cancer declines significantly with increasing breast density and is independently higher in older women with dense breasts. Addition of screening US significantly increases detection of small cancers and depicts significantly more cancers and at smaller size and lower stage than does PE, which detects independently extremely few cancers. Hormonal status has no significant effect on effectiveness of screening independent of breast density.

4. Boyd NF, Guo H, Martin LJ, et al: Mammographic density and the risk and detection of breast cancer. N Engl J Med 356:227-236, 2007.

Background:

Extensive mammographic density is associated with an increased risk of breast cancer and makes

thedetection of cancer by mammography difficult, but the influence of density on risk according to method of cancer detection is unknown.

Methods

We carried out three nested case-control studies in screened populations with 1112 matched case-control pairs. We examined the association of the measured percentage of density in the baseline mammogram with risk of breast cancer, according to method of cancer detection, time since the initiation of screening, and age.

Results

As compared with women with density in less than 10% of the mammogram, women with density in 75% or more had an increased risk of breast cancer (odds ratio, 4.7; 95% confidence interval [CI], 3.0 to 7.4), whether detected by screening (odds ratio, 3.5; 95% CI, 2.0 to 6.2) or less than 12 months after a negative screening examination (odds ratio, 17.8; 95% CI, 4.8 to 65.9). Increased risk of breast cancer, whether detected by screening or other means, persisted for at least 8 years after study entry and was greater in younger than in older women. For women younger than the median age of 56 years, 26% of all breast cancers and 50% of cancers detected less than 12 months after a negative screening test were attributable to density in 50% or more of the mammogram.

Conclusions:

Extensive mammographic density is strongly associated with the risk of breast cancer detected by screening or between screening tests. A substantial fraction of breast cancers can be attributed to this risk factor.

5. Berg WA, Blume JD, Cormack JB, et al. Combined Screening With Ultrasound and Mammography vs Mammography Alone in Women at Elevated Risk of Breast Cancer.JAMA. 2008;299(18):2151-2163.

Context

Screening ultrasound may depict small, node-negative breast cancers not seen on mammography.

Objective

To compare the diagnostic yield, defined as the proportion of women with positive screen test results and positive reference standard, and performance of screening with ultrasound plus mammography vs mammography alone in women at elevated risk of breast cancer.

Design, setting, and participants

From April 2004 to February 2006, 2809 women, with at least heterogeneously dense breast tissue in at least 1 quadrant, were recruited from 21 sites to undergo mammographic and physician-performed ultrasonographic examinations in randomized order by a radiologist masked to the other examination results. Reference standard was defined as a

combination of pathology and 12-month follow-up and was available for 2637 (96.8%) of the 2725 eligible participants.

Main Outcome Measures Diagnostic yield, sensitivity, specificity, and diagnostic accuracy (assessed by the area under the receiver operating characteristic curve) of combined mammography plus ultrasound vs mammography alone and the positive predictive value of biopsy recommendations for mammography plus ultrasound vs mammography alone.

Results

Forty participants (41 breasts) were diagnosed with cancer: 8 suspicious on both ultrasound and mammography, 12 on ultrasound alone, 12 on mammography alone, and 8 participants (9 breasts) on neither. The diagnostic yield for mammography was 7.6 per 1000 women screened (20 of 2637) and increased to 11.8 per 1000 (31 of 2637) for combined mammography plus ultrasound; the supplemental yield was 4.2 per 1000 women screened (95% confidence interval [CI], 1.1-7.2 per 1000; P = .003 that supplemental yield is 0). The diagnostic accuracy for mammography was 0.78 (95% CI, 0.67-0.87) and increased to 0.91 (95% CI, 0.84-0.96) for mammography plus ultrasound (P = .003 that difference is 0). Of 12 supplemental cancers detected by ultrasound alone, 11 (92%) were invasive with a median size of 10 mm (range, 5-40 mm; mean [SE], 12.6 [3.0] mm) and 8 of the 9 lesions (89%) reported had negative nodes. The positive predictive value of biopsy recommendation

after full diagnostic workup was 19 of 84 for mammography (22.6%; 95% CI, 14.2%-33%), 21 of 235 for ultrasound (8.9%, 95% CI, 5.6%-13.3%), and 31 of 276 for combined mammography plus ultrasound (11.2%; 95% CI. 7.8%-15.6%).

Conclusion

Adding a single screening ultrasound to mammography will yield an additional 1.1 to 7.2 cancers per 1000 high-risk women, but it will also substantially increase the number of false positives.

6. **Ellen Warner, Hans Messersmith, Petrina Causer, Andrea Eisen, Rene Shumak, Donald Plewes; Systematic Review: Using Magnetic Resonance Imaging to Screen Women at High Risk for Breast Cancer. Annals of Internal Medicine. 2008 May;148(9):671-679.**

Background:

A sensitive and acceptable screening regimen for women at high risk for breast cancer is essential. Contrast-enhanced magnetic resonance imaging (MRI) of the breast is highly sensitive for diagnosis of breast cancer but has variable specificity.

Purpose:

To summarize the sensitivity, specificity, likelihood ratios, and posttest probability associated with adding MRI to annual mammography screening of women at very high risk for breast cancer.

Data sources:

English-language literature search of the MEDLINE, EMBASE, and Cochrane databases from January 1995 to September 2007, supplemented by hand searches of pertinent articles.

Study selection:

Prospective studies published after 1994 in which MRI and mammography (with or without additional tests) were used to screen women at very high risk for breast cancer.

Data extraction:

Methods and potential biases of studies were assessed by 2 reviewers, and data were extracted and entered into 2 x 2 tables that compared American College of Radiology Breast Imaging Reporting and Data System (BI-RADS) scores of MRI plus mammography, mammography alone, or MRI alone with results of breast tissue biopsies.

Data synthesis:

Eleven relevant, prospective, nonrandomized studies that ranged from small single-center studies with only 1 round of patient screening to large multicenter studies with repeated rounds of annual screening were identified. Characteristics of women that varied across study samples included age range, history of breast cancer, and BRCA1 or BRCA2 mutation status. Studies used dynamic contrast-enhanced MRI with axial or coronal plane images (European studies) or sagittal

images (North American studies) that were usually interpreted without knowledge of mammography results. The summary negative likelihood ratio and the probability of a BI-RADS-suspicious lesion (given negative test findings and assuming a 2% pretest probability of disease) were 0.70 (95% CI, 0.59 to 0.82) and 1.4% (CI, 1.2% to 1.6%) for mammography alone and 0.14 (CI, 0.05 to 0.42) and 0.3% (CI, 0.1% to 0.8%) for the combination of MRI plus mammography, using a BI-RADS score of 4 or higher as the definition of positive.

Limitations

Differences in patient population, center experience, and criteria for positive screening results led to between-study heterogeneity. Data on patients with nonfamilial high risk were limited, and no data were available on recurrence or survival.

Conclusion

Screening with both MRI and mammography might rule out cancerous lesions better than mammography alone in women who are known or likely to have an inherited predisposition to breast cancer.

Role of Breast Imaging in a Newly Diagnosed Case of Breast Cancer:

Routine diagnostic mammography of both breasts is recommended with use of ultrasound in select cases. The ipsilateral mammography can be avoided if the clinical decision of mastectomy has been made.

MRI is not recommended in all patients diagnosed with breast cancer, even when a Breast Conservation Surgery is planned. The COMICE trial is a randomized controlled trial (RCT) which showed that use of MRI in addition to triple assessment does not reduce the reoperation rate in patients undergoing BCT[1]. The MONET trial is also a RCT that shows adverse effect of MRI in the form of increased re-excision rates in patients undergoing MRI.[2]

As regards contralateral breast cancer, the ACRIN 6667 trial shows that MRI detects clinically and mammographically occult breast cancer.[3] However, the results of this study show that of 12.5 % of women needed additional biopsies on the basis of a positive MRI finding of which less than 25% were positive for

cancer (24.8%) ; and out of these just a little over half were positive for invasive cancer, rest being in-situ. A systematic review and meta-analysis of incremental cancer detection and impact on surgical management of MRI breast shows that MRI does detect more cancers than conventional imaging however does not reliably distinguish benign from malignant findings.[4]

Housammi et al recently published an individual patient data meta-analysis evaluating the association between pre-operative breast MRI and local and distant recurrence in patients with breast cancer. Preoperative MRI is not associated with reduced risk of local recurrence or distant recurrence evidenced by the adjusted hazard ratios for MRI for 8 year recurrence free survival.[5]

However, MRI breast is recommended when the diagnosis of Lobular carcinoma is made. It is also useful in cases of Paget's disease with dense breast on mammograms and no identifiable primary, in cases of metastatic axillary adenopathy and negative dense mammograms and as a problem solving modality.

1. **Comparative effectiveness of MRI in breast cancer (COMICE) trial: a randomised controlled trial.Turnbull L, Brown S, Harvey I, Olivier C, Drew P, Napp Vet al. Lancet. 2010 Feb 13;375 (9714): 563-71.**

Abstract

Background:

MRI might improve diagnosis of breast cancer, reducing rates of reoperation. We assessed the clinical efficacy

of contrast-enhanced MRI in women with primary breast cancer.

Methods

We undertook an open, parallel group trial in 45 UK centres, with 1623 women aged 18 years or older with biopsy-proven primary breast cancer who were scheduled for wide local excision after triple assessment. Patients were randomly assigned to receive either MRI (n=816) or no further imaging (807), with use of a minimisation algorithm incorporating a random element. The primary endpoint was the proportion of patients undergoing a repeat operation or further mastectomy within 6 months of random assignment, or a pathologically avoidable mastectomy at initial operation. Analysis was by intention to treat. This study is registered, ISRCTN number 57474502.

Findings:

816 patients were randomly assigned to MRI and 807 to no MRI. Addition of MRI to conventional triple assessment was not significantly associated with reduced a reoperation rate, with 153 (19%) needing reoperation in the MRI group versus 156 (19%) in the no MRI group, (odds ratio 0.96, 95% CI 0.75-1.24; p=0.77).

Interpretation:

Our findings are of benefit to the NHS because they show that MRI might be unnecessary in this population of patients to reduce repeat operation rates, and could assist in improved use of NHS services.

2. **Preoperative MRI and surgical management in patients with nonpalpable breast cancer: the MONET - randomised controlled trial. Peters NH, van Esser S, van den Bosch MA, Storm RK, Plaisier PW, van Dalen T, et al. Eur J Cancer. 2011 Apr; 47(6): 879-86.**

Abstract

Background:

We evaluated whether performing contrast-enhanced breast MRI in addition to mammography and/or ultrasound in patients with nonpalpable suspicious breast lesions improves breast cancer management.

Methods

The MONET - study (MR mammography of nonpalpable breast tumours) is a randomised controlled trial in patients with a nonpalpable BIRADS 3-5 lesion. Patients were randomly assigned to receive routine medical care, including mammography, ultrasound and lesion sampling by large core needle biopsy or additional MRI preceding biopsy. Patients with cancer were referred for surgery. Primary end-point was the rate of additional surgical procedures (re-excisions and conversion to mastectomy) in patients with a nonpalpable breast cancer.

Findings:

Four hundred and eighteen patients were randomised, 207 patients were allocated to MRI, and 211 patients to the control group. In the MRI group 74 patients had

83 malignant lesions, compared to 75 patients with 80 malignant lesions in the control group. The primary breast conserving surgery (BCS) rate was similar in both groups; 68% in the MRI group versus 66% in the control group. The number of re-excisions performed because of positive resection margins after primary BCS was increased in the MRI group; 18/53 (34%) patients in the MRI group versus 6/50 (12%) in the control group (p=0.008). The number of conversions to mastectomy did not differ significantly between groups. Overall, the rate of an additional surgical intervention (BCS and mastectomy combined) after initial breast conserving surgery was 24/53 (45%) in the MRI group versus 14/50 (28%) in the control group (p=0.069).

Interpretation:

Addition of MRI to routine clinical care in patients with nonpalpable breast cancer was paradoxically associated with an increased re-excision rate. Breast MRI should not be used routinely for preoperative work-up of patients with nonpalpable breast cancer

3. **MRI evaluation of the contralateral breast in women with recently diagnosed breast cancer. Lehman CD, Gatsonis C, Kuhl CK, Hendrick RE, Pisano ED, Hanna L, Peacock S, Smazal SF, Maki DD, Julian TB, DePeri ER, Bluemke DA, Schnall MD; ACRIN Trial 6667 Investigators Group. N Engl J Med. 2007 Mar 29; 356 (13): 1295-303.**

Abstract

Background:

Even after careful clinical and mammographic evaluation, cancer is found in the contralateral breast in up to 10% of women who have received treatment for unilateral breast cancer. We conducted a study to determine whether magnetic resonance imaging (MRI) could improve on clinical breast examination and mammography in detecting contralateral breast cancer soon after the initial diagnosis of unilateral breast cancer.

Methods

A total of 969 women with a recent diagnosis of unilateral breast cancer and no abnormalities on mammographic and clinical examination of the contralateral breast underwent breast MRI. The diagnosis of MRI-detected cancer was confirmed by means of biopsy within 12 months after study entry. The absence of breast cancer was determined by means of biopsy, the absence of positive findings on repeat imaging and clinical examination, or both at 1 year of follow-up.

Results:

MRI detected clinically and mammographically occult breast cancer in the contralateral breast in 30 of 969 women who were enrolled in the study (3.1%). The sensitivity of MRI in the contralateral breast was 91%, and the specificity was 88%. The negative predictive

value of MRI was 99%. A biopsy was performed on the basis of a positive MRI finding in 121 of the 969 women (12.5%), 30 of whom had specimens that were positive for cancer (24.8%); 18 of the 30 specimens were positive for invasive cancer. The mean diameter of the invasive tumors detected was 10.9 mm. The additional number of cancers detected was not influenced by breast density, menopausal status, or the histologic features of the primary tumor.

Conclusions:

MRI can detect cancer in the contralateral breast that is missed by mammography and clinical examination at the time of the initial breast-cancer diagnosis.

4. Magnetic resonance imaging screening of the contralateral breast in women with newly diagnosed breast cancer: systematic review and meta-analysis of incremental cancer detection and impact on surgical management. Brennan ME, Houssami N, Lord S, Macaskill P, Irwig L, Dixon JM, Warren RM, Ciatto S. J Clin Oncol. 2009 Nov 20; 27(33): 5640-9.

Abstract

Purpose:

Preoperative magnetic resonance imaging (MRI) is increasingly used for staging women with breast cancer, including screening for occultcontralateral cancer. This article is a review and meta-analysis of studies reporting

contralateral MRI in women with newly diagnosed invasive breast cancer.

Methods

We systematically reviewed the evidence on contralateral MRI, calculating pooled estimates for positive predictive value (PPV), true-positive:false-positive ratio (TP:FP), and incremental cancer detection rate (ICDR) over conventional imaging. Random effects logistic regression examined whether estimates were associated with study quality or clinical variables.

Results:

Twenty-two studies reported contralateral malignancies detected only by MRI in 131 of 3,253 women. Summary estimates were as follows: MRI-detected suspicious findings (TP plus FP), 9.3% (95% CI, 5.8% to 14.7%); ICDR, 4.1% (95% CI, 2.7% to 6.0%), PPV, 47.9% (95% CI, 31.8% to 64.6%); TP:FP ratio, 0.92 (95% CI, 0.47 to 1.82). PPV was associated with the number of test positives and baseline imaging. Few studies included consecutive women, and few ascertained outcomes in all subjects. Where reported, 35.1% of MRI-detected cancers were ductal carcinoma in situ (mean size = 6.9 mm), 64.9% were invasive cancers (mean size = 9.3 mm), and the majority were stage pTis or pT1 and node negative. Effect on treatment was inconsistently reported, but many women underwent contralateral mastectomy.

Conclusion:

MRI detects contralateral lesions in a substantial proportion of women, but does not reliably distinguish benign from malignant findings. Relatively high ICDR may be due to selection bias and/or overdetection. Women must be informed of the uncertain benefit and potential harm, including additional investigations and surgery.

5. **An Individual Person Data Meta-Analysis of Preoperative Magnetic Resonance Imaging and Braest Cancer Recurrence. Houssami N, Turner R, Mcaskill P, Turnbull LW, McCready DR, Tuttle TM, Vapiwala N and Solin LJ. J Clin Oncol 2014 Published online 6 January.**

Abstract

Purpose:

There is liffle consensus regarding preoperative magnetic resonance imaging (MRI) in breast cancer (BC). We examined the association between preoperative MRI and local recurrence (LR) as primary outcome, as well as distant recurrence (DR), in patients with BC.

Methods:

An individual person data (IPD) meta-analysis, based onpreoperative MRI studies that met predefined eligibility criteria, was performed. Survival analysis (Cox proportional hazards modeling) was used to investigate time to recurrence and to estimate the hazard ratio (HR) for MRI. We modeled the univariable association

between LR (or DR) and MRI, and covariates, and fitted multivariable models to estimate adjusted HRs. Sensitivity analysis was based on women who had breast conservation with radiotherapy.

Results:

Four eligible studies contributed IPD on 3,180 affected breasts in 3,169 subjects (median age, 56.2 years). Eight-year LR-free survival did not differ between the MRI (97%) and no-MRI (95%) goups (P = .87), and the multivariable model showed no significant effect of MRI on LR-free suvival: HR for MRI (versus no-MRI) was 0.88 (95% CI, 0.52 to 1.51 P = .65); age, margin status, and tumor grade were associated with LR-free survival (all P< .05). HR for MRI was 0.96 (95% CI, 0.52 to 1.77; P = .90) in sensitivity analysis. Eight-year DR-free survival did not differ between the MRI (89%) and noMRI (93%) groups (P = .37), and the multivariable model showed no significant effect of MRI on DR-free survival: HR for MRI 9v no-MRI) was 1.18 (95% CI, 0.76 to 2.27; P= .48) or 1.31 (95% CI, 0.76 to 2.27; P =.34) in sensitivity analysis.

Conclusion:

Preoperative MRI for staging the cancerous breast does not reduce the risk of LR or DR.

Imaging and Staging of Lung Cancer:

Lung cancer is the third most common cancer and the leading cause of cancer-related death in the United States [13]. In India, approximately 63,000 new lung cancer cases are reported each year [14]. Lung cancers clinically are divided into 2 categories: Small cell lung cancer and Non–small cell lung cancer for the purpose of treatment and prognosis. Small cell lung cancer is considered a systemic disease and these patients are surgical candidates, its clinical course, prognosis and treatment options are different from NSCLC. About 20% of malignant tumors of the lung are small cell carcinoma, and they almost always are metastatic; either to mediastinal nodes or distant metastasis and chemotherapy is the treatment. It categorized as limited disease when the disease is confined to an area of the thorax that can be included in a single radiation portal and the disease is called extensive when the thoracic disease cannot be included in a single radiation portal or there are extrathoracic metastasis. Contrast enhanced

Computed Tomography is necessary to evaluate small cell lung cancer. Non-Small Cell Lung Cancer (NSCLC) needs meticulous staging as the stage of the disease has treatment and prognostic implications. [Refer AJCC 7th Edition (2009) lung cancer staging].

Imaging:

Chest radiograph is often an initial investigation; it is universally available and is inexpensive; however, it is not helpful in picking up early disease and approximately 12 to 30% of lung cancers are missed on chest radiograph. Investigation such as Computed Tomography (CT) is invariably required for better delineation and characterization of abnormalities detected on chest radiographs.

Initial Work-Up:

CT is used to map the complete extent of disease and CT is also useful for CT-guided biopsies. The wide availability of Multi Detector Computed Tomography (MDCT,) has made it the imaging technique of choice for staging lung cancer, as it can cover the entire thorax, including adrenal and liver in a single breath hold. The volume data that is acquired has isotropic voxels and the multiplanar reformations generated from this data set are of excellent quality and virtual bronchoscopy (requires a dedicated software and workstation), a 3D (dimensional) visualization technique that creates images of the inner surface of the tracheobronchial system to obtain a visual impression is also possible with this data set. No

measurements should however be performed on virtual bronchoscopy images; they should be performed on the native CT images. The scanning is performed in caudo-cranial direction to prevent artifacts that result from relatively long breath hold times that may be uncomfortable for sick patients. The intravenous contrast medium is administered at the rate of 3 cc per second, and the volume of contrast is 80 to 100 cc, this administered contrast needs to chased with saline flush, to reduce artifacts that result from excess contrast concentration in the brachiocephalic vein on the side injected. The start delay is 30 seconds, because it leads to better differentiation between tumor and collapsed lung. The optimal acquisition slice thickness is 2.5 or 3.0 mm with a retro-recon of 0.625 or 0.75 mm as these images yield superior detail and yield quality reformations. For staging of peripheral lung carcinoma reformats of 1.25 or 1.5 mm are employed in the region of the tumor, to assess its relation to adjacent structures such as interlobar fissures, bronchi, vessels and pleura. For central tumors or tumors abutting the chest wall, reformatting should be performed in planes that best depict relationship to adjacent structures. CT scans can evaluate local invasion of the chest wall, mediastinum, main stem bronchus, central veins, and arteries.The use of CT workstation is advisable for diagnostic evaluation.

Magnetic Resonance Imaging (MRI) has a role in the evaluation of NSCLC. MRI is particularly useful in the evaluation of the of superior sulcus tumors, as it better demonstrates the invasion of brachial plexus,

brachiocephalic vessels and adjacent vertebral bodies and ribs. It is helpful in identifying the relationship of tumor to structures like pulmonary artery, aorta, carina and mainstem bronchi [11].

PET-CT scanning is useful in the assessment of solitary pulmonary lung nodules, several studies indicate that PET-CT scanning can differentiate between a benign nodule and malignant nodule and it is extremely useful in locoregional staging and distant metastatic disease. PET-CT has greater accuracy than conventional CT chest and is good non-invasive modality for evaluation of lung cancer.

The usefulness and limitations of these imaging modalities in staging of NSCLC:

CT scans are useful in evaluating primary tumors and for noninvasive anatomic evaluation of the hila and mediastinum. The reports in literature indicate that increase in attenuation of 20 HU (Hounsfield Units) or more is 98% sensitive and 73% specific for lung cancer. CT scans may be helpful in demonstrating superior vena cava compression, pericardial effusion, and lymphangitic dissemination.T-staging is best performed with Computed Tomography [6], it depicts the extent of disease quite accurately. It also identifies satellite nodules. CT criteria for lymphadenopathy are based on size alone and do not always accurately reflect the presence or absence of tumor metastases and hence it is unsatisfactory for nodal staging. The sensitivity and specificity of CT in detecting metastatic mediastinal lymph node involvement is 61% and 79% respectively[5]. When enlarged nodes are seen on CT scan, they aid a

surgeon in planning procedures such as mediastinoscopy, mediastinotomy, or percutaneous needle aspiration biopsy, In spite of its shortcomings CT chest provides a useful roadmap for more accurate surgical staging. The chest wall or mediastinal involvement is either under staged or over staged with computed tomography because of its inability to pin-point infiltration, hence the sensivity and specificity of computed tomography is limited.

MRI is superior as compared to CT scan, in the evaluation of the extent of superior sulcus tumors (reported sensitivity of approximately 90% and a specificity of 96-100% for detection of chest wall invasion) and in evaluation of central tumors and their relation to adjacent structures, lack of ionizing radiation and direct multiplanar capability are also an added advantage. The long imaging times though are a deterrent in very sick individuals [11].

FDG PET-CT imaging has higher sensitivity, specificity, and accuracy than does CT scanning in staging mediastinal disease[1,5]. Published studies state a median sensitivity for FDG-PET of 100% and specificity of 78% in patients with enlarged nodes [5], and a median sensitivity and specificity of 82% and 93% in patients with normal sized nodes [5]. PET/CT is perhaps the best noninvasive imaging modality for assessment of NSCLC [1, 5]; however numerous pitfalls exist as increased FDG uptake is not limited to cancer cells, many processes with increased metabolic activity, such as infection and inflammation (such as tuberculosis, histoplasmosis and rheumatoid nodules, show

increased uptake on PET both in the lung as well as nodes and also normal physiologic uptake in brown fat can be misinterpreted as pathology. A source of false negative is the low metabolic activity of tumors such as bronchoalveolar carcinoma, carcinoid, and bronchogenic carcinoma measuring less than 10 mm[5].

The imaging modality of choice for evaluating brain metastasis in lung cancer patients is magnetic resonance imaging, scans must be performed pre contrast and post contrast with intravenous gadolinium. In patients who cannot tolerate MRI examination, contrast enhanced computed tomography is an alternative [1, 10, and 11].

Imaging follow up:

The purpose of post treatment imaging follow up is to detect recurrence. The incidence of recurrence is during the first two years; however there is no consensus on whether CT chest should be routinely used for follow up. It would be ideal to have a baseline post treatment (surgery) CT scan of chest for reference and to perform chest radiography every four months for two years followed by chest radiographs every six months after that, in addition to annual CT chest, this will allow early detection of recurrence as well as early detection a new lung primary. If a new lung primary is detected, it will allow early definitive therapy. The survival is poor either with locoregional or distant recurrence. Thought PET-CT is more sensitive (97 to 100%) than conventional CT chest, its reported specificity is 62 to 100%. False positives with PET-CT are a result of post

treatment (surgery/radiation) inflammatory changes; hence it should be obtained 12 to 16 weeks following therapy.

CT Scan for detection of Lung Cancer (Screening) [3]:

Screening is a strategy to detect disease when it is more likely to be cured. The efficacy of screening program is judged on the basis of how it reduces all-cause mortality (factors the risks associated with interventions) and disease specific mortality in the population that is screened.

The latest recommendations of the American College of Chest Physicians (ACCP) taking cognizance of the findings of National Lung Screening Trial, recommend screening of high risk individuals with low dose computed tomography over screening with chest x ray or no screening if comprehensive care can be provided (Grade 2B) [2, 9, 16]

The US preventive Task Force (USPSTF) in July 2013 has also made a recommendation for screening high risk individuals with low dose computed tomography (Grade B Recommendation) [15].

There are risks associated with screening for lung cancer namely; risk of radiation exposure and false positive and false negative findings, which may result in unnecessary interventions and such findings, can cause anxiety or complacency.

The main benefit of lung cancer screening for high risk individuals is that it detects cancer at an early

when it is curable. Whether lung cancer screening would benefit individuals who have smoked for shorter time periods remains to be seen.

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J Thorac Imaging. 2012 Sep; 27(5):315-24. doi: 10.1097/RTI.0b013e318254a198.

Evidence-based imaging in lung cancer: a systematic review.

Ravenel JG.

Abstract

Lung cancer is the leading cause of cancer-related mortality in the United States. To assess prognosis, optimize treatment, and avoid potentially harmful futile treatments it is critical to have a complete understanding of the tumor's histology, molecular characteristics, and stage at the time of diagnosis. From the radiologist's perspective, the goal is to provide as accurate a stage as possible before the use of minimally invasive or invasive procedures to guide the site of biopsy and confirm a final pathologic stage. This article reviews the evidence behind the imaging technologies used in the staging evaluation of lung cancer.

PMID: 22914125 [Pub Med - indexed for MEDLINE]

Follow-up and surveillance of the patient with lung cancer after curative-intent therapy: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines.

Colt HG, Murgu SD, Korst RJ, Slatore CG, Unger M, Quadrelli S.

Abstract

Background:

These guidelines are an update of the evidence-based recommendations for follow-up and surveillance of

patients after curative-intent therapy for lung cancer. Particular updates pertain to whether imaging studies, health-related quality-of-life (HRQOL) measures, tumor markers, and bronchoscopy improve outcomes after curative-intent therapy.

Methods:

Meta-analysis of Observational Studies in Epidemiology guidelines were followed for this systematic review, including published studies on post treatment outcomes in patients who received curative-intent therapy since the previous American College of Chest Physicians subject review. Four population, intervention, comparison, and outcome questions were formulated to guide the review. The MEDLINE and CINAHL databases were searched from June 1, 2005, to July 8, 2011, to ensure overlap with the search strategies used previously.

Results:

A total of 3,412 citations from MEDLINE and 431 from CINAHL were identified. Only 303 were relevant. Seventy-six of the 303 articles were deemed eligible on the basis of predefined inclusion criteria after full-text review, but only 34 provided data pertaining directly to the subject of the questions formulated to guide this review. In patients undergoing curative-intent surgical resection of non-small cell lung cancer, chest CT imaging performed at designated time intervals after resection is suggested for detecting recurrence. It is recommended that treating physicians who are able

to incorporate the patient's clinical findings into decision-making processes be included in follow-up and surveillance strategies. The use of validated HRQOL instruments at baseline and during follow-up is recommended. Biomarker testing during surveillance outside clinical trials is not suggested. Surveillance bronchoscopy is suggested for patients with early central airway squamous cell carcinoma treated by curative-intent photodynamic therapy and for patients with intraluminal bronchial carcinoid tumor who have undergone curative-intent bronchoscopic treatment with Nd: YAG laser or electrocautery.

Conclusions:

There is a paucity of well-designed prospective studies specifically targeting follow-up and surveillance modalities aimed at improving survival or QOL after curative-intent therapy. Additional research is warranted to clarify which curative-intent treatment modalities affect HRQOL the most and to identify patients who are at the most risk for recurrence or impaired QOL after treatment. Further evidence is needed to determine how the frequency and duration of surveillance programs that include imaging studies, QOL measurements, tumor markers, or bronchoscopy affect patient morbidity, survival, HRQOL, and health-care costs.

PMID: 23649451[Pub Med - indexed for MEDLINE]

N Engl J Med. 2013 May 23; 368(21):1980-91.

Results of initial low-dose computed tomographic screening for lung cancer.

National Lung Screening Trial **Research Team, Church TR, Black WC, Aberle DR, Berg CD, Clingan KL, Duan F, Fagerstrom RM, Gareen IF, Gierada DS, Jones GC, Mahon I, Marcus PM, Sicks JD, Jain A, Baum S.**

Collaborators (44)

Abstract

Background:

Lung cancer is the largest contributor to mortality from cancer. The National Lung Screening Trial (NLST) showed that screening with low-dose helical computed tomography (CT) rather than with chest radiography reduced mortality from lung cancer. We describe the screening, diagnosis, and limited treatment results from the initial round of screening in the NLST to inform and improve lung-cancer-screening programs.

Methods:

At 33 U.S. centers, from August 2002 through April 2004, we enrolled asymptomatic participants, 55 to 74 years of age, with a history of at least 30 pack-years of smoking. The participants were randomly assigned to undergo annual screening, with the use of either low-dose CT or chest radiography, for 3 years. Nodules or other suspicious findings were classified as positive results. This article reports findings from the initial screening examination.

Results:

A total of 53,439 eligible participants were randomly assigned to a study group (26,715 to low-dose CT and 26,724 to chest radiography); 26,309 participants (98.5%) and 26,035 (97.4%), respectively, underwent screening. A total of 7191 participants (27.3%) in the low-dose CT group and 2387 (9.2%) in the radiography group had a positive screening result; in the respective groups, 6369 participants (90.4%) and 2176 (92.7%) had at least one follow-up diagnostic procedure, including imaging in 5717 (81.1%) and 2010 (85.6%) and surgery in 297 (4.2%) and 121 (5.2%). Lung cancer was diagnosed in 292 participants (1.1%) in the low-dose CT group versus 190 (0.7%) in the radiography group (stage 1 in 158 vs. 70 participants and stage IIB to IV in 120 vs. 112). Sensitivity and specificity were 93.8% and 73.4% for low-dose CT and 73.5% and 91.3% for chest radiography, respectively.

Conclusions:

The NLST initial screening results are consistent with the existing literature on screening by means of low-dose CT and chest radiography, suggesting that a reduction in mortality from lung cancer is achievable at U.S. screening centers that have staff experienced in chest CT. (Funded by the National Cancer Institute; NLST Clinical Trials.gov number, NCT00047385.).

JAMA. 2012 Jun 13; 307(22):2418-29.

Benefits and harms of CT screening for lung cancer: a systematic review.

Bach PB, Mirkin JN, Oliver TK, Azzoli CG, Berry DA, Brawley OW, Byers T, Colditz GA, Gould MK, Jett JR, Sabichi AL, Smith-Bindman R, Wood DE, QaseemA, Detterbeck FC.

Abstract

Context:

Lung cancer is the leading cause of cancer death. Most patients are diagnosed with advanced disease, resulting in a very low 5-year survival. Screening may reduce the risk of death from lung cancer.

Objective:

To conduct a systematic review of the evidence regarding the benefits and harms of lung cancer screening using low-dose computed tomography (LDCT). A multisociety collaborative initiative (involving the American Cancer Society, American College of Chest Physicians, American Society of Clinical Oncology, and National Comprehensive Cancer Network) was undertaken to create the foundation for development of an evidence-based clinical guideline.

Data sources:

MEDLINE (Ovid: January 1996 to April 2012), EMBASE (Ovid: January 1996 to April 2012), and the Cochrane Library (April 2012).

Study selection:
Of 591 citations identified and reviewed, 8 randomized trials and 13 cohort studies of LDCT screening met criteria for inclusion. Primary outcomes were lung cancer mortality and all-cause mortality, and secondary outcomes included nodule detection, invasive procedures, follow-up tests, and smoking cessation.

Data extraction:
Critical appraisal using predefined criteria was conducted on individual studies and the overall body of evidence. Differences in data extracted by reviewers were adjudicated by consensus.

Results:
Three randomized studies provided evidence on the effect of LDCT screening on lung cancer mortality, of which the National Lung Screening Trial was the most informative, demonstrating that among 53,454 participants enrolled, screening resulted in significantly fewer lung cancer deaths (356 vs 443 deaths; lung cancer"specific mortality, 274 vs 309 events per 100,000 person-years for LDCT and control groups, respectively; relative risk, 0.80; 95% CI, 0.73-0.93; absolute risk reduction, 0.33%; P = .004). The other 2 smaller studies showed no such benefit. In terms of potential harms of LDCT screening, across all trials and cohorts, approximately 20% of individuals in each round of screening had positive results requiring some degree of follow-up, while approximately 1% had lung cancer. There was marked heterogeneity in this finding and in the frequency of follow-up investigations, biopsies,

and percentage of surgical procedures performed in patients with benign lesions. Major complications in those with benign conditions were rare.

Conclusion:

Low-dose computed tomography screening may benefit individuals at an increased risk for lung cancer, but uncertainty exists about the potential harms of screening and the generalizability of results.

Imaging of Hepatocellular Carcinoma:

Imaging of the liver is performed either to rule out metastasis in patient with known primary or in patients with cirrhosis and /or risk factors for developing hepatocellular carcinoma. Hepatic metastases are commonly seen in patients with renal cancer, breast cancer, gastric cancer, melanoma, neuroendocrine tumors and colorectal cancers. Imaging of liver is performed not only to detect disease but to characterize liver lesions to distinguish liver cancer from other benign focal lesions of the liver and in cases with liver cancer; either primary or metastatic disease to stage disease. It is important to define if a metastasis from colorectal cancer is single and to evaluate its extent, the same holds true for small early hepatocellular carcinoma, as surgery is the best option for such patients. For detection of hepatic metastasis, the CT scan is performed as a survey examination with precontrast scan of the liver, followed by post contrast scan of the liver in the porto-venous phase. If CT scan

of the liver is performed for characterization of lesion/s or for staging of liver lesions, the imaging needs to be performed in arterial, porto-venous and equilibrium phase following intravenous administration of contrast, this should be preceded by non-contrast scan of the liver.

Hepatocellular cancer screening & diagnosis:

Current recommendations for surveillance include AFP and ultrasound performed every 6 months. AFP alone is inadequate for screening. AFP is not sufficiently sensitive or specific to be used as diagnostic assay. The sensitivity of the test is 60%, if 20ng/mL is used as the cut off. Using higher levels of cut off, improves specificity but at the cost of lowering sensitivity even further. The findings of a mass in the liver with elevated Alpha-fetoprotein (AFP) does not indicate HCC as AFP can be raised in intrahepatic cholangiocarcinoma and in metastasis from colon cancer, sometimes. Patients with rising AFP levels should receive further diagnostic imaging.

The reported sensitivity of ultrasound is 65% to 80% as a screening test, but it should be noted that ultrasound is not a diagnostic test. The examination should be performed with careful attention to the liver.

For lesions smaller than 1 cm, detected during screening of patients at high risk for HCC, close follow up, using the same imaging modality that detected the lesions, every 3 months, is recommended **(level of evidence 3ii)*.** If the lesions increase in size to 1 cm

or larger, then contrast enhanced multiphase computed tomography or magnetic resonance imaging should be performed to arrive at a diagnosis.

In patients with cirrhosis or other risk factors for HCC, a triple phase Contrast Enhanced Computed Tomography (CECT) or Dynamic contrast enhanced MRI can reliably diagnose HCC in nodules larger than 1 cm, during arterial phase the HCCs enhance more than the surrounding liver parenchyma and in the venous it shows less enhancement due wash out of contrast, the early arterial enhancement followed by washout, in venous phase, in single a study has a specificity of 95 to 100% for HCC of 1 to 3 cm diameter and is diagnostic of HCC even without biopsy confirmation **(level of evidence 3ii)*,** use of a second imaging modality is not necessary. If in situations where the findings on first modality are atypical and not diagnostic, the second imaging modality (either CT or MRI) can increase sensitivity from 44% to 79% without decrease in specificity when both modalities are used sequentially. If inspite of using two modalities the findings, for a nodule larger than 1 cm, are inconclusive, in patient at high risk for HCC, a liver biopsy needs to be considered and may be performed. If the biopsy is negative, the lesion needs imaging follow up every 3 to 6 months and if the lesion enlarges and if still the imaging findings are atypical a repeat biopsy is recommended.

Of the several staging systems; The Barcelona-Clinic Liver Cancer system is the most commonly used, as it can predict survival.

*National Cancer Institute: PDQ® Liver (Hepatocellular) Cancer Screening. Bethesda, MD: National Cancer Institute. Date last modified 05/23/2013.

Available at :http://cancer.gov/cancertopics/pdq/screening/hepatocellular/Health Professional. Accessed on 01/01/2014. [Case series =3 (population-based 3i, non-population based consecutive 3ii, non-population based non-consecutive 3iii)]

Suggested Reading:

Imaging of hepatocellular carcinoma: diagnosis, staging and treatment monitoring.

Hennedige T, Venkatesh SK.

Source

Diagnostic Imaging, National University Hospital, National University Health System, Singapore.

Abstract

Hepatocellular carcinoma (HCC) is the most common primary liver cancer. Imaging is important for establishing a diagnosis of HCC. Several imaging modalities including ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET) and angiography are used in evaluating patients with chronic liver disease and suspected HCC. CT, MRI and contrast-enhanced US have replaced biopsy for diagnosis of HCC. Dynamic multiphase contrast-enhanced CT or MRI is the current standard for imaging diagnosis of HCC. Functional imaging techniques such as perfusion

CT and diffusion-weighted MRI provide additional information about tumor angiogenesis that may be useful for treatment. Techniques evaluating tissue mechanical properties such as magnetic resonance elastography, and acoustic radiation force impulse imaging are being explored for characterizing liver lesions. The role of PET in the evaluation of HCC is evolving with promise seen especially with the use of a hepatocyte-specific PET tracer. Imaging is also critical for assessment of treatment response and detection of recurrence following locoregional treatment. Knowledge of the post-treatment appearance of HCC is essential for correct interpretation.

This review article provides an overview of the role of imaging in the diagnosis, staging and post-treatment follow-up of HCC.

Acta Radiol. 2013 Oct;54(8):843-50. doi: 10.1177/0284185113485571. Epub 2013 May 9.

Optimal scan timing of hepatic arterial-phase imaging of hypervascular hepatocellular carcinoma determined by multiphasic fast CT imaging technique.

Kagawa Y, Okada M, Yagyu Y, Kumano S, Kanematsu M, Kudo M, Murakami T.

Abstract

Background:

A new multiphasic fast imaging technique, known as volume helical shuttle technique, is a breakthrough for liver imaging that offers new clinical opportunities

in dynamic blood flow studies. This technique enables virtually real-time hemodynamics assessment by shuttling the patient cradle back and forth during serial scanning.

Purpose:

To determine optimal scan timing of hepatic arterial-phase imaging for detecting hypervascular hepatocellular carcinoma (HCC) with maximum tumor-to-liver contrast by volume helical shuttle technique.

Material and Methods:

One hundred and one hypervascular HCCs in 50 patients were prospectively studied by 64-channel multidetector-row computed tomography (MDCT) with multiphasic fast imaging technique. Contrast medium containing 600 mg iodine per kg body weight was intravenously injected for 30 s. Six seconds after the contrast arrival in the abdominal aorta detected with bolus tracking, serial 12-phase imaging of the whole liver was performed during 24-s breath-holding with multiphasic fast imaging technique during arterial phase. By placing regions of interest in the abdominal aorta, portal vein, liver parenchyma, and hypervascular HCCs on the multiphase images, time-density curves of anatomical regions and HCCs were composed. Timing of maximum tumor-to-liver contrast after the contrast arrival in the abdominal aorta was determined.

Results:

For the detection of hypervascular HCC at arterial phase, mean time and value of maximum tumor-to-

liver contrast after the contrast arrival were 21 s and 38.0 HU, respectively.

Conclusion:

Optimal delay time for the hepatic arterial-phase imaging maximizing the contrast enhancement of hypervascular HCCs was 21 s after arrival of contrast medium in the abdominal aorta.

Keywords:

Abdomen/GI, CT, hemodynamics/flow dynamics, liver PMID: 23761547 [PubMed - indexed for MEDLINE] AJR Am J Roentgenol. 2008 Sep;191(3):772-7. doi: 10.2214/AJR.07.3452.

Optimal arterial phase imaging for detection of hypervascular hepatocellular carcinoma determined by continuous image capture on 16-MDCT.

Ma X, Samir AE, Holalkere NS, Sahani DV.

Abstract

Objective:

The purpose of this study is to estimate the optimal time delay before the initiation of arterial phase scanning for detection of hypervascular hepatocellular carcinoma (HCC) on 16-MDCT when a rapid bolus injection of contrast medium is administered.

Subjects and Methods:

In this prospective study, 25 patients (19 men and six women; mean age, 63.5 years; age range, 50-81 years)

with pathologically confirmed HCC were included. Dynamic 16-MDCT imaging was performed in cine mode using 70 mL of nonionic iodinated contrast medium (300 mg I/mL) at an injection rate of 7 mL/s. Four consecutive 5-mm-thick slices at the maximum diameter of the HCC were selected as the region of interest. Time-attenuation curves were generated by region of interest drawn on the aorta, tumor, and liver. Qualitative assessments of conspicuity for contrast medium wash-in, peak, and wash-out of aorta and tumor were performed.

Results:

There were 108 arterial phase enhancing lesions (mean [+/-SD], 4.9 +/- 2.4 cm; range, 0.7-12.9 cm) in the 25 patients. The maximum Hounsfield value of aorta, tumor, and background liver parenchyma were 463.8 +/- 98 HU, 106.5 +/- 19 HU, and 98.3 +/- 14 HU, respectively. At the time of onset of peak tumor enhancement, the difference between tumor density and background liver density was 38.2 +/- 19 HU. The time-attenuation curve showed that the mean times of contrast enhancement start, peak, and end were 9.2 +/- 2.7 seconds, 19.4 +/- 2.1 seconds, and 38 +/- 13.5 seconds, respectively, for the aorta, and 15.5 +/- 2.6 seconds, 26.3 +/- 2.9 seconds, and 57.7 +/- 14.4 seconds, respectively, for 25 pathologically confirmed hepatocellular carcinomas. Qualitatively, the mean times of contrast enhancement wash-in, peak, and washout were 10.2 +/- 2.8 seconds, 19.9 +/- 3 seconds, and 39.9 +/- 9.2 seconds, respectively for the aorta, and 18 +/- 4.2 seconds, 27 +/- 3 seconds, and

55.7 +/- 21 seconds, respectively, for tumor. There were no differences between quantitative and qualitative measurements of wash-in and peak time for the aorta (p = 0.00017, p = 0.00016) and tumor (p = 0.00163, p = 0.00040).

Conclusion:
When using 70 mL of 300 mg I/mL of contrast medium with an injection rate of 7 mL/s in 16-MDCT scanning, the optimal time to initiate scanning for HCC is 26.3 +/- 2.9 seconds (range, 24.0-34.5 seconds) after contrast medium administration.

PMID: 18716108 [PubMed - indexed for MEDLINE]

Semin Oncol. 2012 Aug; 39(4):399-409. doi: 10.1053/j.seminoncol.2012.05.010.

Diagnosis of hepatocellular carcinoma: newer radiological tools.

Lee JM, Yoon JH, Kim KW.

Abstract

With the recent dramatic advances in diagnostic modalities, the diagnosis of hepatocellular carcinoma (HCC) is primarily based on imaging. Ultrasound (US) plays a crucial role in HCC surveillance. Dynamic multiphasic multidetector-row CT (MDCT) and magnetic resonance imaging (MRI) are the standard diagnostic methods for the noninvasive diagnosis of HCC, which can be made based on hemodynamic features (arterial enhancement and delayed washout). The technical development of MDCT and MRI has made

possible the fast scanning with better image quality and resolution, which enables an accurate CT hemodynamic evaluation of hepatocellular tumor, as well as the application of perfusion CT and MRI in clinical practice. Perfusion CT and MRI can measure perfusion parameters of tumor quantitatively and can be used for treatment response assessment to anti-vascular agents. Besides assessing the hemodynamic or perfusion features of HCC, new advances in MRI can provide a cellular information of HCC. Liver-specific hepatobiliary contrast agents, such as gadoxetic acid, give information regarding hepatocellular function or defect of the lesion, which improves lesion detection and characterization. Diffusion-weighted imaging (DWI) of the liver provides cellular information of HCC and also has broadened its role in lesion detection, lesion characterization, and treatment response assessment to chemotherapeutic agents. In this article, we provide an overview of the state-of-the art imaging techniques of the liver and their clinical role in management of HCC.

PMID: 22846858 [PubMed - indexed for MEDLINE]

Locoregional Therapies in Hepatobiliary Malignancies

Locoregional therapies in HCC: Role of Interventional Radiology.

Introduction

Surgical resection remains the standard of care for patients with hepatocellular carcinoma with single lesion and well preserved liver function with 5-year survival rates of at least 50%–70%. Less than 30% of patients are suitable or fit for surgery at presentation which has made several locoregional therapies an attractive and reliable alternative to resection. It offers a useful adjunct in oncological treatment of HCC patient as a bridge to definitive liver transplant or resection while also aiding in palliative disease control in unresectable HCC. Interventional Radiology plays a vital role in offering various loco-regional therapies.

Diagnostic algorithm:

- A focal liver lesion in a patient with cirrhosis is highly likely to be a HCC.
- A raised serum Alfa Feto Protein (AFP) level confirms the diagnosis and further investigations are only required to guide selection of the most appropriate therapy.
- If AFP is normal, further imaging with Triphasic CT, MRI or Lipiodol CT will allow a confident diagnosis of HCC to be made, thus obviating the need for a biopsy.
- Biopsy is rarely required for the diagnosis and is best avoided especially in the potentially resectable lesions in view of tumor seeding in the biopsy tract.

The HCC management algorithm is guided by the BCLC guidelines (Figure 1) and it is mandatory that patients undergo a formal multidisciplinary evaluation prior to initiating any such treatment in order to ascertain the best available treatment options for individual patients.

Table 1 : Locoregional liver directed therapies

A. Percutaneous ablative therapies :

I. Chemical ablation :
   a. Percutaneous ethanol injection (PEI).
   b. Percutaneous acetic acid injection.

II. Thermal ablation :
   a. Radiofrequency Ablation (RFA)
   b. Microwave Ablation (MW)
   c. Irreversible electroporation (IRE)
   d. Laser Ablation

Table 1 : Locoregional liver directed therapies

e. Cryo Ablation
f. HIFU (High Intensity Focused Ultrasound)

B. Transarterial Therapies:

a. Transarterial chemo-embolisation (TACE)
b. Transarterial bland-embolisation (TAE)
c. Transarterial Radioembolisation (TARE)
d. Transarterial chemoinfusion (TACI)

C. Miscellaneous :

a. Portal vein embolization.

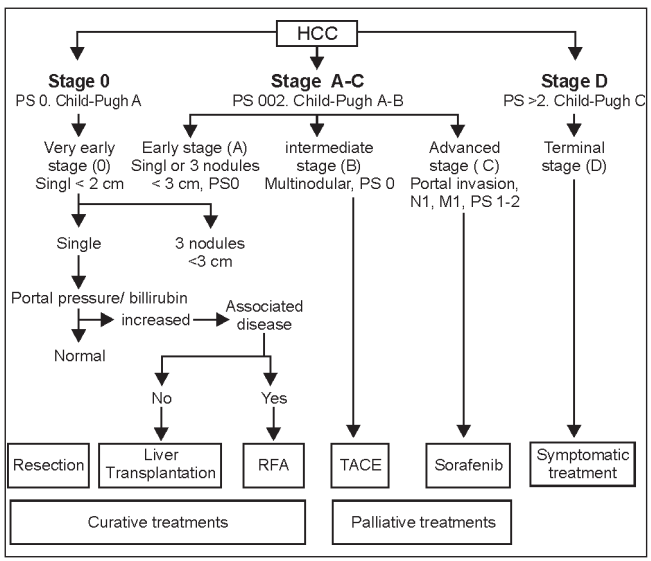

Figure 1: The BCLC staging system for HCC. PS - Performance Status; RFA - Radiofrequency Ablation; TACE - Transarterial Chemoembolization.

Image-Guided percutaneous ablation:

Image-guided percutaneous ablation is currently accepted as the treatment of choice for nonsurgical patients for 'Very Early' and 'Early Stage' of HCC as per BCLC guidelines. Among ablative techniques, radiofrequency ablation is the most widely used. Targeting of the lesion can be performed under ultrasound, CT or MRI guidance. Real-time ultrasound/ CT or (ultrasound/MRI) fusion imaging is also reliable tool.

RFA involves ablation of neoplastic tissue by direct intralesional thermo coagulation.

RFA can be performed with a monopolar or a bipolar electrode system. In a monopolar system, the circuit is completed through the patient's body whereas in the bipolar system it is completed locally.

Pre-treatment assessment:

- Tissue diagnosis or convincing clinical diagnosis.(e.g. liver mass in a patient with HBV infection with raised AFP)
- Cross sectional imaging of abdomen and pelvis.(CT or MRI). PET CT in patient with liver metastasis.
- Exclusion of extra-hepatic disease
- Laboratory evaluation:
  - ✓ Routine haematological evaluation.
  - ✓ Coagulation profile.
  - ✓ Biochemical parameters – LFT, RFT, SE.
  - ✓ Tumor marker (AFP)

Patient Selection for RFA

HCC :

1. Solitary HCC less than or equal to 3 cm in size.
2. Solitary HCC less than or equal to 5 cm in size. The chances of residual unabated tumor are higher in patients with tumors larger than 3 cm therefore these patients need to be treated with some other locorectonal therapy like chemoembolization for adequate local control of disease.
3. RFA can also be extended to patients who have upto 3 tumors in the liver provided all are 3 cm or less in size.

Metastases:

1. Patients with liver dominant or liver only disease are eligible for RFA provided the number of lesions is 3 or less. Size cut-off of 3 cm also applies to liver metastases to ensure complete ablation.
2. Anatomical or functional imaging (PET scan) should be done to exclude extrahepatic disease.

Important strategies for RFA :

1. Ablation of small lesions which are seen only on arterial phase may be difficult. A lipiodol CT done prior to RFA may help localize the lesion due to lipiodol retention within the tumor.
2. Overlapping ablations:Creation of multiple overlapping ablation zones is required to cover larger lesions.

3. Ablation of subcapsular lesions: Can be done.The RFA tract should be preferably through liver parenchyma.
4. Ablation close to vessels: Large blood vessels carry away heat and interfere with the efficacy of ablation.Temporary balloon occlusion of the portal vein or hepatic artery have been described to create larger ablation zones.These maneuvers are seldom necessary in practice.

Ablation end-points:

Most important measure is the maintainance of target temperature throughout the duration of RFA. Uniformity in the target temperature throughout the lesion is desirable to ensure uniform ablation. Immediate fall in the temperatures within 30 sec after RFA may suggest a need for reablation.

Track ablation:

This is a critical step in RFA as it ensures that the potential of needle tract seeding is avoided. Track ablation should also be done if the needle position has to be adjusted prior to RFA.

Monitoring completeness of RFA:

Immediate post procedure imaging:

Local vascular complications like hematomas, arterial pseudoaneurysm and portal vein thrombosis must be looked for.

A thin rim of enhancement surrounding the zone of ablation and outlining the ablation track is the usual

finding and represents the inflammatory response to RFA.

This has been termed benign perilesional enhancement and is the imaging equivalent of complete ablation.

Nodular rim enhancement or persistent arterial phase enhancement is suggestive of residual tumor.

Surveillance:

Imaging:

Response:

1. Absence of internal enhancement
2. Reduction in size of the lesion
3. Retraction of hepatic capsule.

Recurrence:

1. Nodular rim enhancement
2. I nternal enhancement.

Tumor Markers :Appropriate tumor marker levels are evaluated.A decreasing trend in the tumor marker levels is suggestive of response to RFA.

Complications:

1. Arterial injury leading to pseudoaneurysms and perihepatic hematomas may need emergent angiography and embolisation.
2. Portal vein thrombosis
3. Perihepatic collections
4. Bile duct injury.

The ablation protocol including target temperature and time duration for ablation will depend upon the target tissue and will vary according to the RFA system that is being used. For complete coverage of the lesion and achieving total necrosis, a 1cm margin of tissue on all sides of the lesion should be ablated.

Safety and efficacy of RFA

Cancer. 2005 Mar 15;103(6):1201-9.

Percutaneous radiofrequency ablation for hepatocellular carcinoma. An analysis of 1000 cases.

Tateishi R, Shiina S, Teratani T, Obi S, Sato S, Koike Y, Fujishima T, Yoshida H, Kawabe T, Omata M.

Background:

Radiofrequency ablation (RFA) was introduced recently as a therapeutic modality for hepatocellular carcinoma (HCC), an alternative to percutaneous ethanol injection therapy (PEIT), which is coming into use worldwide. Previously reported treatment efficacy and complication rates have varied considerably.

Methods:

Between February 1999 and February 2003, the authors performed 1000 treatments of RFA to 2140 HCC nodules in 664 patients with a cooled-tip electrode at the University of Tokyo Hospital (Tokyo, Japan). Short-term and long-term complications were analyzed by treatment and session basis. Cumulative survival was also assessed in 319 patients who received RFA as

primary treatment (naive patients) and 345 patients who received RFA for recurrent tumor after previous treatment including resection, PEIT, microwave coagulation therapy, and transarterial embolization (nonnaive patients).

Results:

A total of 40 major complications (4.0% per treatment, 1.9% per session) and 17 minor complications (1.7% per treatment, 0.82% per session) were observed during the observation period until March 31, 2004. There were no treatment-related deaths. Surgical intervention was required in one case each of bile peritonitis and duodenal perforation. The cumulative survival rates at 1, 2, 3, 4, and 5 years were 94.7%, 86.1%, 77.7%, 67.4%, and 54.3% for naive patients, whereas the cumulative survival rates were 91.8%, 75.6%, 62.4%, 53.7%, and 38.2% for nonnaive patients, respectively.

Conclusions:

The authors confirmed the safety and efficacy of RFA for HCC in a large-scale series and long-term prognosis was satisfactory.

American Journal of Surgery 2004 Dec;70(12):1035-8.

Radio-frequency ablation of large, nonresectable hepatic tumors.

Morgan JH 3rd, Royer GM, Hackett P, Gamblin TC, McCampbell BL, Conforti A, Dale PS.

Patients with nonresectable hepatic metastases who are not treated survive an average of 6 months. We

report our experience with radio-frequency ablation (RFA) of nonresectable hepatic tumors 4 cm or greater in size. A retrospective chart review of all patients undergoing RFA of hepatic tumors 4 cm or greater from October 1, 1999, through August 31, 2002, was performed. Thirty-six patients were identified who underwent RFA of tumors 4 cm or greater. There were a total of 81 tumors ablated in the 36 patients. Twenty patients underwent RFA only; seven patients received RFA plus a wedge resection. Five patients were treated with RFA followed by chemoembolization. Two patients underwent RFA plus placement of a hepatic artery infusion pump. The median tumor size was 5 cm (range, 4-14 cm). Median patient follow-up was 26 months (range, 1-54 months). Patients with metastatic colon cancer had the longest median survival of 28 months (range, 1 and 48 months). The survival of primary hepatocellular carcinoma was worse with a median survival of 20 months (range, 1-36 months). At last follow-up, 11 (30%) of the patients remain alive and disease free. There were no perioperative deaths and one intraoperative complication. In our experience, RFA of larger tumors is effective and safe. Tumor size should not be an absolute contraindication to RFA of nonresectable hepatic tumors.

Liver Transplantation 2005 Sep;11(9):1117-26.

Percutaneous ablation procedures in cirrhotic patients with hepatocellular carcinoma submitted to liver transplantation: Assessment of efficacy at explant analysis and of safety for tumour

recurrence Pompili M, Mirante VG, Rondinara G, Fassati LR, Piscaglia F, Agnes S, Covino M, Ravaioli, M, Fagiuoli S, Gasbarrini G, Rapaccini GL.

Aims of this retrospective study were to analyze the efficacy and safety of percutaneous ethanol injection (PEI) and radiofrequency ablation (RFA) in cirrhotic patients with hepatocellular carcinoma (HCC) submitted to orthotopic liver transplantation (OLT). We studied 40 patients undergoing OLT in whom 46 HCC nodules had been treated with PEI (13 nodules), RFA (30 nodules), or PEI+RFA (3 nodules). Child-Turcotte-Pugh class was A in 18 cases, B in 18, and C in 4. The mean waiting time for OLT was 9.5 months. The effectiveness of ablation techniques was evaluated by histological examination of the explanted livers. Complete necrosis was found in 19 nodules (41.3%), partial or absent necrosis in 27 nodules (58.7%). Among the 30 nodules treated by RFA, 14 were completely necrotic (46.7%) and 16 demonstrated partial necrosis (53.3%). Considering the 13 neoplasms undergoing PEI, 3 nodules showed complete necrosis (23.1%), 6 partial necrosis (46.1%), and 4 absent necrosis (30.8%). The rate of complete necrosis was 53.1% for nodules smaller than 3 cm and 14.3% for larger lesions (P = 0.033) but increased to 61.9% when considering only the lesions smaller than 3 cm treated by RFA. During the follow up, HCC recurred in 3 patients treated by PEI. No cases of HCC recurrence at the abdominal wall level were recorded. Percutaneous ablation procedures are effective treatments in cirrhotic patients with HCC submitted to OLT and are not associated to an increased risk of tumor recurrence. RFA provides

complete necrosis in most nodules smaller than 3 cm, and appears to be the best treatment option in these cases.

Radiology. 2000 March; 214(3) : 761-8.

Hepatocellular carcinoma: radio-frequency ablation of medium and large lesions.

Livraghi T, Goldberg SN, Lazzaroni S, Meloni F, Ierace T, Solbiati L, Gazelle GS.

Purpose:

To study local therapeutic efficacy, side effects, and complications of radio-frequency (RF) ablation in the treatment of medium and large hepatocellular carcinoma (HCC) lesions in patients with cirrhosis or chronic hepatitis. MATERIALS AND Methods:

One-hundred fourteen patients who were under conscious sedation or general anesthesia had 126 HCCs greater than 3.0 cm in diameter treated with RF by using an internally cooled electrode. Eighty tumors were medium (3.1-5.0 cm), and 46 were large (5.1-9.5 cm). The mean diameter for all tumors was 5.4 cm. At imaging, 75 tumors were considered noninfiltrating, and 51 were considered infiltrating.

Results:

Complete necrosis was attained in 60 lesions (47.6%), nearly complete (90%-99%) necrosis in 40 lesions (31.7%), and partial (50%-89%) necrosis in the remaining 26 lesions (20.6%). Medium and/or noninfiltrating tumors were treated successfully

significantly more often than large and/or infiltrating tumors. Two major complications (death, hemorrhage requiring laparotomy) and five minor complications (self-limited hemorrhage, persistent pain) were observed. The single death was due to a break in sterile technique rather than to the RF procedure itself.

Conclusions: RF ablation appears to be an effective, safe, and relatively simple procedure for the treatment of medium and large HCCs.

Percutaneous RFA is a safe and effective treatment modality for liver tumors. It can be applied to small as well as large tumors. The ability to induce complete necrosis appears to be limited by size and proximity to blood vessels.

RFA vs Surgical Resection

Hepatology. 2008 Jan; 47(1):82-9.

Sustained complete response and complications rates after radiofrequency ablation of very early hepatocellular carcinoma in cirrhosis: Is resection still the treatment of choice?

Livraghi T, Meloni F, Di Stasi M, Rolle E, Solbiati L, Tinelli C, Rossi S.

If liver transplantation is not feasible, partial resection is considered the treatment of choice for hepatocellular carcinoma (HCC) in patients with cirrhosis. However, in some centers the first-line treatment for small, single, operable HCC is now radiofrequency ablation (RFA). In the current study, 218 patients with single HCC <or= 2.0 cm (very early or T1 stage) underwent RFA.

We assessed 2 primary end points that could be easily compared with those reported for resective surgery: (1) the rate of sustained, local, complete response and (2) the rate of treatment-related complications. The secondary end point was 5-year survival in the 100 patients whose tumors had been considered potentially operable. After a median follow-up of 31 months, sustained complete response was observed in 216 patients (97.2%). In the remaining 6, percutaneous ethanol injection, selective intraarterial chemoembolization, or resection were used as salvage therapy. Perioperative mortality, major complication, and 5-year survival rates were 0%, 1.8%, and 68.5%, respectively. Conclusion: Compared with resection, RFA is less invasive and associated with lower complication rate and lower costs. RFA is also just as effective for ensuring local control of stage T1 HCC, and it is associated with similar survival rates (as recently demonstrated by 2 randomized trials). These data indicate that RFA can be considered the treatment of choice for patients with single HCC <or= 2.0 cm, even when surgical resection is possible. Other approaches can be used as salvage therapy for the few cases in which RFA is unsuccessful or unfeasible.

Korean Journal of Hepatology. 2005 March;11(1):59-71.

The comparative results of radiofrequency ablation versus surgical resection for the treatment of hepatocellular carcinoma.

Cho CM, Tak WY, Kweon YO, Kim SK, Choi YH, Hwang YJ, Kim YI.

Background/Aims :
Although surgical resection remains the gold standard of therapy for hepatocellular carcinoma (HCC), only selected patients can undergo resection because of the severity of the underlying cirrhosis or due to the diffuse distribution of the tumor. Radiofrequency ablation (RFA) has recently shown comparable results to surgical resection for the treatment of HCC. We compared the results of RF ablation and surgical resection for the treatment of HCC.

Methods:
From January 2000 to December 2002, one hundred-sixty patients who had undergone surgical resection or RFA were analyzed retrospectively. The patients with a tumor size less than 5 cm in diameter, with less than 3 tumors in number, with tumor having a Child-Pugh class A classification and no evidence of extrahepatic metastasis were enrolled in the study. The recurrence pattern was classified into local and distant recurrence. We compared the recurrence patterns, the survival rates, the recurrence rates and the complications between the two groups.

Results:
1) The local recurrence rate was 9.8% for surgical resection and 18.2% for RFA and the distant recurrence rate were 32.8% and 28.3%, respectively. 2) The 1-, 2- and 3-year overall cumulative survival rates after RFA

and surgery were 95.8%, 86.8%, 80.0%, 98.3%, 87.0% and 77.4%, respectively. 3) The incidence of complication was similar between the two groups.

Conclusions:

Radiofrequency ablation shows comparable results to surgical resection for the treatment of HCC. Therefore, RFA should be considered as the treatment of choice those patients who are not candidates for resection. However, intrahepatic recurrence of tumor after RFA was as frequent as that seen after surgical resection. Further investigation is warranted to clarify whether the current RFA technology could offer improved long-term results.

Survival rates and patterns and rates of local and distant intrahepatic recurrences appear to compare favourably between resection and RFA for HCC.RFA has an advantage of low morbidity and repeatability over surgery and appears to be the treatment of choice for recurrent HCC after resection. Surgery appears to be superior to RFA for colorectal metastases.

LONG TERM OUTCOMES IN RFA

European Journal of Radiology 2007 August 30

Radiofrequency ablation of hepatocellular carcinoma: Long-term outcome and prognostic factors.

Yan K, Chen MH, Yang W, Wang YB, Gao W, Hao CY, Xing BC, Huang XF.

Purpose:

To investigate the efficacy of radiofrequency ablation (RFA) for hepatocellular carcinoma (HCC), and the prognostic factors for post-RFA survival rate. Methods:

From 1999 to 2006, 266 patients with 392 HCCs underwent ultrasound guided RFA treatment. They were 216 males and 50 females, average age 59.4+/-15.4 years (24-87 years). The HCC were 1.2-6.7cm in diameters (average 3.9+1.3cm). There were 158 patients with single tumor, and the rest had multiple (2-5) tumors. Univariate and multivariate analysis with 19 potential variables were examined to identify prognostic factors for post-RFA survival rate.

Results:

The overall post-RFA survival rates at 1st, 3rd, and 5th year were 82.9%, 57.9% and 42.9%, respectively. In the 60 patients with stage I HCC (AJCC staging), the 1-, 3-, 5-year survival rate were 94.8%, 76.4% and 71.6%, significantly higher than the 148 patients with stage II-IV tumors (81.8%, 57.6% and 41.2%, P=0.006). For the 58 patients with post-surgery recurrent HCC, the survival rates were 73.2%, 41.9% and 38.2% at the 1st, 3rd, and 5th year, which were significantly lower than those of stage I HCC (P=0.005). Nine potential factors were found with significant effects on survival rate, and they were number of tumors, location of tumors, pre-RFA liver function enzymes, Child-Pugh classification, AJCC staging, primary or recurrent HCC, tumor pathological grading, using mathematical protocol in RFA procedure and tumor necrosis 1 month

after RFA. After multivariate analysis, three factors were identified as independent prognostic factors for survival rate, and they were Child-Pugh classification, AJCC staging and using mathematical protocol.

Conclusions:

Identifying prognostic factors provides important information for HCC patient management before, during and after RFA. This long-term follow-up study on a large group of HCC patients confirmed that RFA could not only achieve favourable outcome on stage I HCC, but also be an effective therapy for stage II-IV or recurrent HCC.

Annals of Surgery 2007 October;246(4):559-65;

Survival after radiofrequency ablation of colorectal liver metastases : 10-year experience.
Siperstein AE, Berber E, Ballem N, Parikh RT.

Objective:

To assess factors affecting long-term survival of patients undergoing radiofrequency ablation (RFA) of colorectal hepatic metastases, with attention to evolving chemotherapy regimens.

Methods:

Prospective evaluation of 235 patients with colorectal metastases who were not candidates for resection and/or failed chemotherapy underwent laparoscopic RFA. Preoperative risk factors for survival and pre- and postoperative chemotherapy exposure were analyzed.

Results:

Two hundred and thirty-four patients underwent 292 RFA sessions from 1997 to 2006, an average of 8 months after initiation of chemotherapy. Twenty-three percent had extrahepatic disease preoperatively. Patients averaged 2.8 lesions, with a dominant diameter of 3.9 cm. Kaplan-Meier actuarial survival was 24 months, with actual 3 and 5 years survival of 20.2% and 18.4%, respectively. Median survival was improved for patients with <or=3 versus >3 lesions (27 vs. 17 months, P=0.0018); dominant size<3 versus >3 cm (28 vs. 20 months, P=0.07); chorioembryonic antigen<200 versus >200 ng/mL (26 vs. 16 months, P=0.003). Presence of extrahepatic disease (P=0.34) or type of pre/postoperative chemotherapy (5-FU-leucovorin vs. FOLFOX/FOLFIRI vs. bevacizumab) (P=0.11) did not alter median survival.

Conclusions:

To our knowledge, this is both the largest and longest follow up of RFA for colorectal metastases. The number and dominant size of metastases, and preoperative chorioembryonic antigen value are strong predictors of survival. Despite classic teaching, extrahepatic disease did not adversely affect survival. In this group of patients who failed chemotherapy, newer treatment regimens (pre- or postoperatively) had no survival benefit. The actual 5-year survival of 18.4% in these patients versus near zero survival for chemotherapy alone argues for a survival benefit of RFA.

Annals of Surgical Oncology. 2005 August ; 12(8):616-28

Significant long-term survival after radiofrequency ablation of unresectable hepatocellular carcinoma in patients with cirrhosis.

Raut CP, Izzo F, Marra P, Ellis LM, Vauthey JN, Cremona F, Vallone P, Mastro A, Fornage BD, Curley SA.

Background:

Radiofrequency ablation (RFA) offers an alternative treatment in some unresectable hepatocellular carcinoma (HCC) patients with disease confined to the liver. We prospectively evaluated survival rates in patients with early-stage, unresectable HCC treated with RFA.

Methods:

All patients with HCC treated with RFA between September 1, 1997, and July 31, 2002, were prospectively evaluated. Patients were treated with RFA by using a percutaneous or open Intraoperative approach with ultrasound guidance and were evaluated at regular intervals to determine disease recurrence and survival.

Results:

A total of 194 patients (153 men [79%] and 41 women [21%]) with a median age of 66 years (range, 39-86 years) underwent RFA of 289 sonographically detectable HCC tumors. All patients were followed up

for at least 12 months (median follow-up, 34.8 months). Percutaneous and open Intraoperative RFA was performed in 140 (72%) and 54 (28%) patients, respectively. The median diameter of tumors treated with RFA was 3.3 cm. Disease recurred in 103 (53%) of 194 patients, including 69 (49%) of 140 patients treated percutaneously and 34 (63%) of 54 treated with open RFA (not significant). Local recurrence developed in nine patients (4.6%). Most recurrence was intrahepatic. The overall complication rate was 12%. Overall survival rates at 1, 3, and 5 years for all 194 patients were 84.5%, 68.1%, and 55.4%, respectively.

Conclusions:

Treatment with RFA can produce significant long-term survival rates for cirrhotic patients with early-stage, unresectable HCC. RFA can be performed in these patients with relatively low complication rates. Confirmation of these results in randomized trials should be considered.

RFA alone or in combination with other modalities gives satisfactory long term survival advantage to patients with unresectable HCC.

RFA AS A BRIDGE TO TRANSPLANTATION

Annals of Surgery. 2004 November;240(5):900-9.

Radiofrequency ablation of small hepatocellular carcinoma in cirrhotic patients awaiting liver transplantation: a prospective study.

Mazzaferro V, Battiston C, Perrone S, Pulvirenti A, Regalia E, Romito R, Sarli D, Schiavo M,

Garbagnati F, Marchianò A, Spreafico C, Camerini T, Mariani L, Miceli R, Andreola S.

Objective:

Determine the histologic response-rate (complete versus partial tumor extinction) after single radiofrequency ablation (RFA) of small hepatocellular carcinoma (HCC) arising in cirrhosis. Investigate possible predictors of response and assess efficacy and safety of RFA as a bridge to liver transplantation (OLT).

Results:

Mean interval RFA—>OLT was 9.5 months. Post-RFA complete response rate was 55%, rising to 63% for HCC </=3 cm. Tumor size was the only prognostic factor significantly related to response (P = 0.007). Tumor satellites and/or new HCC foci (56 nodules) were unaffected by RFA and significantly correlated with HCC >3 cm (P = 0.05). Post-RFA tumor persistence probability increased with time (12 months: 59%; 18 months: 70%). Radiologic response rate was 70%, not significantly different from histology. Major post- RFA morbidity was 8%. No mortality, Child deterioration, patient withdrawal because of tumor progression was observed. Post-OLT 3-year patient/graft survival was 83%.

Conclusions:

RFA is a safe and effective treatment of small HCC in cirrhotics awaiting OLT, although tumor size (>3 cm) and time from treatment (>1 year) predict a high risk of tumor persistence in the targeted nodule. RFA should not be considered an independent therapy for HCC.

American Journal of Roentgenology 2006 May;186 (5 Suppl) : S296-305.

Percutaneous radiofrequency ablation for hepatocellular carcinoma before liver transplantation: a prospective study with histopathologic comparison.

Brillet PY, Paradis V, Brancatelli G, Rangheard AS, Consigny Y, Plessier A, Durand F, Belghiti J, Sommacale D, Vilgrain V.

Objective:

The aims of this study were to determine the feasibility and efficacy of Percutaneous radiofrequency ablation in patients with hepatocellular carcinoma waiting for liver transplantation and to compare the radiologic and pathologic findings.

Results:

Percutaneous radiofrequency ablation was performed in 21 (81%) patients for 28 tumors. Both minor and major complications occurred in three patients (10% each per session). The rates of primary technique effectiveness, secondary technique effectiveness for percutaneous radiofrequency ablation alone (seven tumors), and combined percutaneous radiofrequency ablation and transcatheter arterial chemoembolization (three tumors) were 56%, 76%, and 86%, respectively. After a mean follow-up of 11.9 months, 16 patients (76%) received transplants, whereas five patients were excluded from the waiting list because of distant tumor progression (n =3, 14%) or other causes (n = 2, 10%). After transplantation, tumor recurred in one (6%) of

16 patients. Histopathologic examinations were performed for 13 (81%) of 16 patients and showed complete necrosis and satellite nodules in, respectively, 12 (75%) and seven (44%) of 16 tumors.

Conclusions: Percutaneous radiofrequency ablation can be performed on hepatocellular carcinoma patients waiting for transplantation, allows most patients to undergo transplantation, and does not impair post transplantation outcomes. The procedure produces complete necrosis of the treated tumor in most cases but is associated with a high rate of satellite nodules.

RFA appears to be an effective modality as a bridge to transplantation.

RFA OF SUBCAPSULAR TUMORS

American Journal of Radiology 2006; 186:S269–S274

Percutaneous Radiofrequency Ablation Therapy of Hepatocellular Carcinoma Using Multitined Expandable Electrodes: Comparison of Subcapsular and Nonsubcapsular Tumors

Yun Ku Cho, Hyunchul Rhim, Yong Sik Ahn1, Mi Young Kim and Hyo Keun Lim

Objective:

Our objective was to compare the prognosis of subcapsular and nonsubcapsular hepatocellular carcinoma after percutaneous radiofrequency ablation using multitined expandable electrodes.

Results:

No significant differences in initial complete ablation rate (100% vs 96.7%, p = 1.000) or local tumor progression rate (0% vs 10.0%, p = 0.545) were found between subcapsular and nonsubcapsular tumors. No procedure-related major complication or mortality occurred. The overall 1- and 3-year survival rates were 89.3% and 60.3%, respectively.

Conclusions The rates of local tumor progression and complications for radiofrequency ablation using multitined expandable electrodes for subcapsular hepatocellular carcinomas were comparable to those for nonsubcapsular hepatocellular carcinomas.

RFA of subcapsular tumors can be safely performed. The efficacy and complication rates are not different than that for non-subcapsular tumors.

RFA FOR METASTASES

Radiology. 2001 October ;221(1):159-66.

Percutaneous radio-frequency ablation of hepatic metastases from colorectal cancer: long-term results in 117 patients.

Solbiati L, Livraghi T, Goldberg SN, Ierace T, Meloni F, Dellanoce M, Cova L, Halpern EF, Gazelle GS.

Purpose:

To describe the results of an ongoing radio-frequency (RF) ablation study in patients with hepatic metastases from colorectal carcinoma.

Results:

Estimated median survival was 36 months (95% CI; 28, 52 months). Estimated 1, 2, and 3-year survival rates were 93%, 69%, and 46%, respectively. Survival was not significantly related to number of metastases treated. In 77 (66%) of 117 patients, new metastases were observed at follow-up. Estimated median time until new metastases was 12 months (95% CI; 10, 18 months). Percentages of patients with no new metastases after initial treatment at 1 and 2 years were 49% and 35%, respectively. Time to new metastases was not significantly related to number of metastases. Seventy (39%) of 179 lesions developed local recurrence after treatment. Of these, 54 were observed by 6 months and 67 by 1 year. No local recurrence was observed after 18 months. Frequency and time to local recurrence were related to lesion size (P < or =.001).

Conclusions:

RF ablation is an effective method to treat hepatic metastases from colorectal carcinoma.

Surgery. 2007 July;142 (1):10-9.

Laparoscopic radiofrequency ablation of neuroendocrine liver metastases: a 10- year experience evaluating predictors of survival.

Mazzaglia PJ, Berber E, Milas M, Siperstein AE.

Background:

A decade ago we reported the first use of laparoscopic radiofrequency thermal ablation (RFA) for the treatment

of neuroendocrine hepatic metastases. This study analyzes our 10-year experience and determines characteristics predictive of survival.

Results:

There were 22 women and 41 men, age 54.4 +/- 1.5 years followed for 2.8 +/- 0.3 years (range, 0.1 to 7.8). Tumor types included 36 carcinoid, 18 pancreatic islet cell, and 9 medullary thyroid cancer. RFA was performed 1.6 +/- 0.3 years after the diagnosis of liver metastases. Number of lesions treated was 6 +/- 0.5 (range, 1 to 16). Forty-nine patients underwent 1 ablation session, and 14 (22%) had repeat sessions caused by disease progression. Mean hospital stay was 1.1 days. Perioperative morbidity was 5%, with no 30-day mortality. Fifty-seven percent of patients exhibited symptoms. One week postoperatively 92% of these reported at least partial symptom relief, and 70% had significant or complete relief. Duration of symptom control was 11 +/- 2.3 months. CT follow-up demonstrated 6.3% local tumor recurrence. Larger dominant liver tumor size and male gender adversely impacted survival ($P < .05$). Median survival times were 11.0 years post diagnosis of primary tumor, 5.5 years post diagnosis of neuroendocrine hepatic metastases, and 3.9 years post-1st RFA. Survival for patients undergoing repeat ablation sessions was not significantly lower.

Conclusions:

This study represents the largest series of neuroendocrine hepatic metastases treated by RFA. In

this group of patients with aggressive neuroendocrine tumor metastases and limited treatment options, RFA provides effective local control with prompt symptomatic improvement.

RFA of liver metastases is safe and effective in properly selected patients.

European Journal of Radiology. 2007 December

Comparison of FDG-PET, PET/CT and MRI for follow-up of colorectal liver metastases treated with radiofrequency ablation: Initial results.

Kuehl H, Antoch G, Stergar H, Veit-Haibach P, Rosenbaum-Krumme S, Vogt F, Frilling A, Barkhausen J, Bockisch A..

Purpose:

Morphologic imaging after radiofrequency ablation (RFA) of liver metastases is hampered by rim-like enhancement in the ablation margin, making the identification of local tumor progression (LTP) difficult. Follow-up with PET/CT is compared to follow-up with PET alone and MRI after RFA.

Methods and Materials:

Sixteen patients showed 25 FDG positive colorectal liver metastases in pre-interventional PET/CT. Post-interventional PET/CT was performed 24h after ablation and was repeated after 1, 3 and 6 months and then every 6 months. PET and PET/CT data were compared with MR data sets acquired within 14 days before or after these time points. Either histological proof by biopsy or resection, or a combination of contrast

enhanced CT at fixed time points and clinical data served as a reference.

Results:

The 25 metastases showed a mean size of 20mm and were treated with 39 RFA sessions. Ten lesions which developed LTP received a second round of RFA; four lesions received three rounds of treatment. The mean follow-up time was 22 months. Seventy-two PET/CT and 57 MR examinations were performed for follow-up. The accuracy and sensitivity for tumor detection was 86% and 76% for PET alone, 91% and 83% for PET/CT and 92% and 75% for MRI, respectively.

Conclusions:

In comparison to PET alone, PET/CT was significantly better for detecting LTP. After RFA, there were no significant differences between MRI and PET/CT.

European Journal of Radiology. 2004 Jun;51 Suppl:S19-23.

Guidance and monitoring of radiofrequency liver tumor ablation with contrast-enhanced ultrasound.

Solbiati L, Ierace T, Tonolini M, Cova L.

Radiofrequency (RF) treatments of non-resectable hepatic tumors are generally guided with real-time sonography, which, however, cannot differentiate necrotic changes from viable tumor. To achieve complete treatment of hepatic tumors, accurate imaging techniques are needed for close treatment follow-up. Usually contrast-enhanced computed tomography (CT)

and magnetic resonance imaging (MRI) are used; however, they can be performed only at the end of treatment sessions. In this field, contrast-enhanced ultrasound (CEUS) has shown to improve the sensitivity of plain ultrasonography. Recently, further developments of contrast-enhanced US technique have significantly increased its clinical utility. Continuous mode, low MI scans performed with harmonic imaging and contrast specific software appears as a very useful technique for the visualization of both macro- and microcirculation with depiction of tumor vascularisation. In our hospital, we have been employing contrast-enhanced sonography with sulphur hexaflouride microbubbles (SonoVue, Bracco, Italy) before, during and immediately at the end of RF ablation procedures to monitor and assess the therapeutic result prior to closing the treatment session. The results obtained in a group of 109 patients with hepatocellular carcinoma (HCC) in liver cirrhosis (192 lesions) and in 53 patients with liver metastases (97 lesions) undergoing a single session of percutaneous RF tumor ablation, showed that the sensitivity of CEUS for the detection of residual tumor was almost equivalent to that of contrast-enhanced helical CT. More importantly, since the introduction of intraoperative CEUS the rate of partially unablated tumors has dropped from 16.1 to 5.9%. Cost-effectiveness and reduction of patients' discomfort related to the need of re-treatment are the two most outstanding advantages of CEUS in this field.

Ultrasound Med Biol. 2007 Nov;33(11):1736-49.

Comparison of contrast enhanced ultrasound and contrast enhanced CT or MRI in monitoring percutaneous thermal ablation procedure in patients with hepatocellular carcinoma: a multi-center study in China.

Lu MD, Yu XL, Li AH, Jiang TA, Chen MH, Zhao BZ, Zhou XD, Wang JR.

Authors evaluated the ability of contrast enhanced ultrasound (CEUS) in monitoring percutaneous thermal ablation procedure in patients with hepatocellular carcinoma (HCC) in comparison with contrast enhanced computed tomography (CECT) and/or magnetic resonance imaging (CEMRI). A total of 151 patients were enrolled in the study. Before the radio-frequency (RF) or microwave ablation treatment, tumor vascularity was assessed in 139 patients with three imaging modalities i.e., US (139 exams), CEUS (139 exams) and CECT (103 exams)/CEMR (36 exams). CEUS examination was performed using a sulphur hexafluoride-filled microbubble contrast agent (SonoVue((R)), Bracco, Milan, Italy) and real-time contrast-specific imaging techniques. Within 30 +/-7 d after the ablation procedure, 118/139 patients were monitored to assess the tumor response to treatment. Before ablation, contrast enhancement within tumor was observed in 129/139 (92.8%) patients with CEUS and 133/139 (95.7%) patients with CECT/CEMRI. Compared with CECT/CEMRI, CEUS sensitivity and accuracy in detecting tumor vascularity were 97.0% and 94.2%, respectively. One month after treatment,

no enhancement was seen in 110/118 (93.2%) both on CEUS and CECT/CEMRI. Concordance between CEUS and CECT/CEMR on the presence of residual vascularization was obtained in four patients (true positive). The specificity and accuracy of CEUS in detecting tumor vascularity were 98.2% and 96.6%, respectively. The periprocedural impact of SonoVue administration on the assessment of treatment extent was also evaluated in a subgroup of patients and CEUS showed its superiority compared with baseline US in defining treatment outcome. In conclusion, in the detection of HCC tumor vascularity and assessment of response to thermal ablation after 1 month, real time CEUS provided results comparable to those obtained with CECT/CEMRI. CEUS examination proved to be a safe and easy to access procedure, with potential for diagnostic impact in the clinical practice.

Microwave Ablation

The electromagnetic (Microwave) energy is passed into the cells resulting in rapid rotation of water molecules in the cells culminating in thermotoxic injury to the cells issue in the viscinity of the applied microwave electrode.

Yamashiki et al reported complete ablation in 89% using microwave ablation (14). Dong et al reported 3yr & 5yr survival rates of 73% & 57% respectively (15) in patients treated by microwave ablation.

Shibata et al did not find statistically significant difference in efficacy between RF ablation and Microwave ablation in their randomized control trial

involving 72 patients with 94 HCC nodules. However, RFA was found to be superior with regard to local recurrence & complications rates (17).

Laser Ablation

Ablation is achieved with light energy applied via fibers inserted directly into the tissue. The efficacy of laser ablation was studied in 74 patients of early stage HCC and the overall survival rates at 3yrs & 5yrs were 68% & 15% respectively (18).

J Vasc Interv Radiol 2009; 20:225–234

Laser Ablation of Liver Metastases from Colorectal Cancer with MR Thermometry: 5-Year Survival.

Ralf Puls, Soenke Langner, Christian Rosenberg, Katrin Hegenscheid, Jens Peter Kuehn, Kai Noeckler, and Norbert Hosten

Purpose :

To determine technical success, technique effectiveness, complications, and survival after laser ablation of liver metastases from colorectal cancer.

MethodS :

Eighty-seven consecutive patients (65 men and 22 women; mean age, 62.8 years) with 180 liver metastases from colorectal carcinoma were included between 1998 and 2005. They underwent laser ablation with magnetic resonance (MR) thermometry in 170 sessions. Indications for laser ablation were locally unresectable tumors (16.1%), metastases in both liver lobes (34.5%),

and refusal of surgery and/or general contraindications to surgery (49.4%). Technical success, technique effectiveness, and complication and survival rates were evaluated retrospectively.

Results :

Technical success was achieved in 178 of 180 sessions (99%). Follow-up after 24–48 hours demonstrated an effectiveness rate of 85.6%. Local tumor progression rate was 10% after 6 months. Major complications included large pleural effusion, large subcapsular hematoma, abscess, large pneumothorax, pleuritis with fever, intrahepatic hemorrhage, and biloma. Mean survival from the time of diagnosis of the primary tumor was 50.6 months for all patients treated (95% CI, 44.9–56.3 months). Median survival time was 54 months and survival rates were 95.7% at 1 year, 86.2% at 2 years, 72.4% at 3 years, 50.1% at 4 years, and 33.4% at 5 years. The mean survival time after the first treatment was 31.1 months (95% CI, 26.9–35.3 months).

Conclusions:

Laser ablation of liver metastases of colorectal cancer with MR thermometry appears safe and efficacious. Although the results are encouraging, direct comparison with other ablative modalities in a prospective clinical trial would be necessary to definitely show one modality is superior.

Cryoablation

The basic principle of cryoablation is rapid cooling of the tissue to a lethal temperature, thawing, and repetition of the freeze-thaw cycle resulting tumoricidal effect. Helling et al however found disturbingly high incidence of recurrence at the cryoablated site and there are conflicting reports concerning long-term survival.

Journal of Vascular and Interventional Radiology (2013) Volume 24, Issue 4, Suppl, S44.

Retrospective analysis of percutaneous cryoablation of hepatocellular carcinoma (HCC) in liver.

J.R. Daniels, M. Katz, M. Wallman

Purpose :

Percutaneous cryoablation of hepatocellular carcinoma (HCC) was performed with the intention of comparing our experience with published outcomes for radiofrequency ablation (RFA). We hypothesized that our target recurrence rate for cryoablation would be equivalent or superior to RFA due to precise visualization of margins (iceball) during ablation.

Methods :

Cryoablation was used to treat 35 lesions in 27 patients with HCC limited to the liver. An average of 2.7 cryoprobes (range 1-5) achieved an estimated margin of at least 0.5 cm after two 10 minute freeze-thaw cycles to -40□C. Initial patient and tumor characteristics,

initial blood tests, treatment complications, tumor response and time to tumor failure, transplant or death were evaluated.

Results :

Response was evaluable in 23 patients. Complete response rate was 90.3% after initial treatment and 96.8% after one additional ablation for missed margin in 2 patients. There were no subsequent recurrences in any target lesion. Median follow-up for all patients is 678 days (range 15-1388). Four patients died within 54 days: 2 following intraperitoneal hemorrhage controlled with transarterial embolization, 1 from ischemic liver injury following a TIPS for hydrothorax, and 1 resulting from extra-hepatic abscess. Two patients had recurrent tumor near the ablation tract. Three additional patients had peritoneal hemorrhage not requiring treatment. Risk of bleeding was associated with ascites (P = 0.0129) and albumin level (P=0.0177).

Conclusion :

While excellent tumor control was achieved with cryoablation, morbidity and mortality limit use of cryoablation without technique and equipment modification to avoid hemorrhage and needle tract contamination with tumor.

Irreversible Electroporation

Irreversible electroporation (IRE) is a novel method of destroying the cell using a powerful electrical field of high-voltage direct current (up to 3 kV) which creates multiple holes in the cell membrane and cell death.

IRE overcomes the head sink effect seen in RFA while treating the tumors close blood vessels.

Journal of Vascular and Interventional Radiology 2011 May;22(5):611-21.

Investigation of the safety of irreversible electroporation in humans.

Thomson KR, Cheung W, Ellis SJ, Federman D, Kavnoudias H, Loader-Oliver D, Roberts S, Evans P, Ball C, Haydon A.

Methods:

A single-centre prospective nonrandomized cohort study was performed to investigate the safety of irreversible electroporation (IRE) for tumor ablation in humans.

Methods:

Thirty-eight volunteers with advanced malignancy of the liver, kidney, or lung (69 separate tumors) unresponsive to alternative treatment were subjected to IRE under general anesthesia. Clinical examination, biochemistry, and computed tomography (CT) scans of the treated organ were performed before, immediately after, and at 1 month and 3 months after the procedure.

Results:

No mortalities occurred at 30 days. Transient ventricular arrhythmia occurred in four patients, and electrocardiographically (ECG) synchronized delivery was used subsequently in the remaining 30 patients,

with two further arrhythmias (supraventricular tachycardia and atrial fibrillation). One patient developed obstruction of the upper ureter after IRE. One adrenal gland was unintentionally directly electroporated, which produced transient severe hypertension. There was no other evidence of adjacent organ damage related to the electroporation. Other adverse events were not directly related to IRE, but two patients developed temporary neurapraxia as a result of arm extension during a prolonged period of anesthesia. Although not a primary aim of this preliminary study, complete target tumor ablation verified by CT was achieved in 46 of the 69 tumors treated with IRE (66%). Most treatment failures occurred in renal and lung tumors. Biopsy in three patients showed coagulative necrosis in the regions treated by IRE.

Conclusions:

IRE appears to be safe for human clinical use provided ECG-synchronized delivery is used. Comparative evaluation with alternative ablative technologies is warranted.

Transarterial therapies for liver tumors :

Liver has dual blood supply with majority of liver tumor deriving blood supply from the hepatic artery making transarterial therapy safe and effective in locoregional disease control by delivering the chemo embolic mixture directly into the tumor bed while limiting the damage to the surrounding normal liver parenchyma.

Transarterial chemoembolisation (TACE)

TACE has become the mainstay and preferred treatment for unresectable HCC and is also employed as an adjunctive therapy to liver resection or as a bridge to liver transplantation. It may be combined with ablative therapy. Chemoembolisation for liver tumor may be achieved by Lipiodol TACE (Conventional TACE) or by Drug eluting beads (DEB TACE). Various drugs like doxorubicin, cisplatin, mitomycin C, epirubicin and mitoxantrone have been used for TACE. Post chemoinfusion, the tumor feeders are embolized using gelfoam or particulate embolic agents to induce ischemic tumor necrosis. Drug-eluting microspheres are made of polyvinyl alcohol hydro gel which sequester chemotherapeutic drug from the solution and cause a controlled and sustained release of drug into tumor bed over a long period of time as compared with more rapid release of agents from lipiodol solution in conventional TACE therapy.

Indications :

1) Is a standard for intermediate/advanced stage unresectable HCC even in the setting of portal vein involvement (excluding main portal vein).
2) Helps in predicting tumor biology thereby helping in better patient selection for liver transplantation.
3) As a bridge to transplant for locoregional disease control while the patient is on the waiting list of Liver transplant
4) To down stage patients to resectable or transplantable size criteria

Contra-indications:

1) Poor performance score (ECOG>2)
2) Uncorrectable coagulopathy
3) Advanced liver disease (Child – Pugh C)
4) Significant extra hepatic disease.
5) Underlying infection
6) Anaphylactic reaction to contrast or chemotherapeutic agents.

Portal vein thrombosis is considered as a relative contraindication for TACE.

Survival benefit of Chemoembolisation.

Hepatology 2002; 35:1164-71.

Randomized controlled trial of transarterial lipiodol Chemoembolisation for unresectable hepatocellular carcinoma.

Lo CM, Ngan H, Tso WK, Liu CL, Lam CM, Poon RT, Fan ST, Wong J

This randomized, controlled trial assessed the efficacy of transarterial Lipiodol chemoembolization in patients with unresectable hepatocellular carcinoma. From March 1996 to October 1997, 80 out of 279 Asian patients with newly diagnosed unresectable hepatocellular carcinoma fulfilled the entry criteria and were randomly assigned to treatment with chemoembolization using a variable dose of an emulsion of cisplatin in Lipiodol and gelatin-sponge particles injected through the hepatic artery (chemoembolization group, 40 patients) or

symptomatic treatment (control group, 40 patients). One patient assigned to the control group secondarily was excluded because of unrecognized systemic metastasis. Chemoembolization was repeated every 2 to 3 months unless there was evidence of contraindications or progressive disease. Survival was the main end point. The chemoembolization group received a total of 192 courses of chemoembolization with a median of 4.5 (range, 1-15) courses per patient. Chemoembolization resulted in a marked tumor response, and the actuarial survival was significantly better in the chemoembolization group (1 year, 57%; 2 years, 31%; 3 years, 26%) than in the control group (1 year, 32%; 2 years, 11%; 3 years,3%; P =.002). When adjustments for baseline variables that were prognostic on univariate analysis were made with a multivariate Cox model, the survival benefit of chemoembolization remained significant (relative risk of death, 0.49; 95% CI, 0.29-0.81; P =.006). Although death from liver failure was more frequent in patients who received chemoembolization, the liver functions of the survivors were not significantly different. In conclusion, in Asian patients with unresectable hepatocellular carcinoma, transarterial Lipiodol Chemoembolisation significantly improves survival and is an effective form of treatment.

Lancet. 2002; 359:1734–1739.

Arterial embolisation or Chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomized controlled trial.

Llovet JM, Real MI, Montana X, et al.

A randomized trial was done with the aim of documenting the survival advantage of chemoembolization in patients with unresectable hepatocellular carcinoma. Patients were randomized to receive repeated arterial embolisation with gelatin sponge or chemoembolization with doxorubicin and gelatin sponge. A third group of patients received conservative treatment. A total of 903 patients were assessed and 112 patients were finally included in the study. The primary endpoint was survival. Analyses were by intention to treat.The trial was stopped when the ninth sequential inspection showed that chemoembolization had survival benefits compared with conservative treatment (hazard ratio of death 0·47 [95% CI 0·25–0·91], p=0·025). 25 of 37 patients assigned embolisation, 21 of 40 assigned chemoembolization, and 25 of 35 assigned conservative treatment died. Survival probabilities at 1 year and 2 years were 75% and 50% for embolisation; 82% and 63% for chemoembolization, and 63% and 27% for control (chemoembolization vs. control p=0·009). Chemoembolization induced objective responses sustained for at least 6 months in 35% (14) of cases, and was associated with a significantly lower rate of portal-vein invasion than conservative treatment. Treatment allocation was the only variable independently related to survival (odds ratio 0·45 [95% CI 0·25–0·81], p=0·02). Chemoembolization improved survival of stringently selected patients with unresectable hepatocellular carcinoma. There was no significant difference in the outcome between chemoembolization and bland embolisation groups.

Gastroenterology. 2006 Aug;131(2):461-9.

Prospective cohort study of transarterial chemoembolization for unresectable hepatocellular carcinoma in 8510 patients.

Takayasu K, Arii S, Ikai I, Omata M, Okita K, Ichida T, Matsuyama Y, Nakanuma Y, Kojiro M, Makuuchi M, Yamaoka Y

Aim:

To elucidate the survival of the patients with unresectable hepatocellular carcinoma (HCC) who underwent transcatheter arterial lipiodol chemoembolization (TACE) and to analyze the factors affecting the survivals.

Results:

For overall survival rates by TACE, median and 1-, 3-, 5-, and 7-year survivals were 34 months, 82%, 47%, 26%, and 16%, respectively. Both the degree of liver damage and the tumor-node-metastasis (TNM) system proposed by the Liver Cancer Study Group of Japan demonstrated good stratification of survivals (P = .0001). The multivariate analyses showed significant difference in degree of liver damage (P = .0001), alpha-fetoprotein value (P = .0001), maximum tumor size (P = .0001), number of lesions (P = .0001), and portal vein invasion (P = .0001). The last 3 factors could be replaced by TNM stage. The TACE-related mortality rate after the initial therapy was .5%.

Conclusions:

TACE showed safe therapeutic modality with a 5-year survival of 26% for unresectable HCC patients. The

degrees of liver damage, TNM stage, and alpha-fetoprotein values were independent risk factors for patient survival.

Chemoembolisation is a safe and effective procedure for palliative treatment of unresectable HCC. It offers a survival advantage to patients with HCC.

Chemoembolization in patients with portal vein thrombosis

Journal of Vascular Interventional Radiology ; 4:347-51.

***Hepatic chemoembolization: safety with portal vein thrombosis*.**

Pentecost MJ, Daniels JR, Teitelbaum GP, Stanley P

The authors treated 9 patients with unresectable hepatic malignancy and portal vein thrombosis with hepatic chemoembolization using 10 mg/mL of cross-linked collagen, 10 mg/mL of mitomycin, 3 mg/mL of doxorubicin, and 3 mg/mL of cisplatin. Six patients had primary malignancies (hepatocellular carcinoma in five, hepatoblastoma in one), and three had metastatic tumor (adenocarcinoma of the colon in two, glucagonoma in one). Each patient was treated until flow in the hepatic artery ceased completely. All treatments were technically successful. Eight patients responded to treatment, including two long-term survivors (> 2 years). One patient died 31 days after treatment of progressive hepatic malignancy and atherosclerotic disease. No patient developed hepatic infarction or insufficiency as a result of treatment.

Follow-up ranged from 1 to 26 months (mean, 13 months). The authors conclude that portal vein thrombosis should not be considered an absolute contraindication to hepatic chemoembolization. Hepatic chemoembolization can be performed safely in the presence of adequate collateral circulation.

Journal of Vascular and Interventional Radiology 2014 Jan; 25 (1):32-40.

Transcatheter arterial chemoembolization for advanced hepatocellular carcinoma with portal vein invasion: safety, efficacy, and prognostic factors.

Chern MC, Chuang VP, Liang CT, Lin ZH, Kuo TM

Purpose:

To evaluate the safety and efficacy of transarterial chemoembolization and to identify the prognostic factors associated with survival in patients with hepatocellular carcinoma (HCC) and portal vein (PV) invasion.

Methods:

From January 2006 to March 2012, 50 patients with HCC invading into the PV (Barcelona Clinic Liver Cancer stage C) were treated with transarterial chemoembolization. The parenchymal tumor and PV tumor were confirmed by multidetector computed tomography (CT) and angiography. There were 14 patients with right PV tumor, 12 patients with left PV tumor, and 24 patients with main PV tumor. The response was evaluated by multidetector CT using

Response Evaluation Criteria in Solid Tumors. Patients with residual tumors received repeated transarterial chemoembolization every 6-8 weeks unless the patients achieved complete remission or developed contraindications.

Results:

The median survival period of the entire group was 6.2 months (range, 1.7-50.9 mo), and the overall response rate was 42% (21 of 50 patients). The 6-month, 12-month, 24-month, and 36-month survival rates were 54%, 22%, 10%, and 8%. There were no instances of 30-day mortality or acute liver failure related to transarterial chemoembolization. The median survival of the 21 responders was 10.5 months, and the median survival of the 29 nonresponders was 5.5 months ($P < .001$). In both univariate and multivariate analyses, only the response to transarterial chemoembolization (hazard ratio = 0.25, $P < .001$) and the absence of ascites (hazard ratio = 0.24, $P = .01$) were significant prognostic factors.

Conclusions:

Transarterial chemoembolization is a safe and effective treatment for HCC with major PV invasion. The response to transarterial chemoembolization and the ascites status were the most significant predictive factors for prolonged survival.

Chemoembolisation can be safely performed in patients with portal vein thrombosis in the presence of adequate collateral circulation. A superselective segmental approach is mandatory to reduce the incidence of complications of TACE in this subset of patient.

Chemo embolization as a bridge to transplantation

Am J Transplant. 2007 Aug;7(8):1875-81.

Treatment of HCC in patients awaiting liver transplantation.

Schwartz M, Roayaie S, Uva P.

Liver transplantation (LT) is the treatment of choice for many patients with unresectable hepatocellular carcinoma (HCC), but long waiting time due to the shortage of donor organs can result in tumor progression and drop-out from LT candidacy. Furthermore, even in candidates meeting the restrictive Milan criteria there is risk of HCC recurrence; this risk rises significantly when patients with more advanced HCC are included. In an effort to address these issues, treatment of HCC in patients awaiting LT has become widespread practice. In this review the various modalities employed in the pre-LT setting are presented, and the evidence for benefit with regard to (1) improvement of post-LT survival, (2) down-staging of advanced HCC to within Milan criteria and (3) preventing waiting list drop-out is considered. Chemoembolization, radiofrequency ablation and ethanol injection all have well-documented antitumor activity; however, there is no high level evidence that waiting list HCC treatment with these modalities is effective in achieving any of the three above-mentioned aims. Nevertheless, particularly in the United States, where continued waiting list priority depends on maintaining HCC within Milan criteria, use of

nonsurgical HCC treatment will likely continue in an effort to forestall tumor progression and waiting list drop-out.

Liver Transplantation 2006 Aug;12(8):1260-7.

Response to transarterial chemoembolization as a biological selection criterion for liver transplantation in hepatocellular carcinoma.

Otto G, Herber S, Heise M, Lohse AW, Mönch C, Bittinger F, Hoppe-Lotichius M, Schuchmann M, Victor A, Pitton M.

Criteria to select patients with hepatocellular carcinoma (HCC) for liver transplantation (LT) are based on tumor size and number of nodules rather than on tumor biology. The present study was undertaken to assess the role of transarterial chemoembolization (TACE) in selecting patients with tumors suitable for LT. Ninety-six consecutive patients with HCC were treated by repeatedly performed TACE, 62 of them exceeding the Milan criteria. Patients meeting the Milan criteria were immediately listed, and patients beyond the listing criteria were listed upon downstaging of the tumor following successful TACE. Fifty patients were finally transplanted. Of these 50 patients, 34 exceeded the Milan criteria. In these 96 patients, overall 5-year survival was 51.9%. However, it was 80.9% for patients undergoing LT and 0% for patients without transplantation ($P < 0.0001$). Tumor recurrence was primarily influenced by the control of the disease through continued TACE during the waiting time. Freedom from recurrence after 5 years was 94.5% in patients ($n = 39$) with progress-free TACE during the

waiting time. Tumor recurrence was significantly higher in patients (n = 11) who after initial response to TACE progressed again before LT (freedom from recurrence 35.4%; P = 0.0017). Progress-free course of TACE during the waiting time (P = 0.006; risk ratio, 8.95), and a limited number of tumor nodules as assessed in the surgical specimen (P = 0.025; risk ratio, 0.116) proved to be significant predictors for freedom from recurrence in the multivariate analysis. Milan criteria were without impact on recurrence. Our data suggest that sustained response to TACE is a better selection criterion for LT than the initial assessment of tumor size or number.

Studies suggest a role for TACE in patients awaiting transplantation or resection. Patients responding to TACE appear to have a better long term survival.

Drug eluting beads

Journal of Hepatology 2007 Mar;46(3):474-81. Epub 2006 Nov 29.

Chemoembolization of hepatocellular carcinoma with drug eluting beads: efficacy and doxorubicin pharmacokinetics.

Varela M, Real MI, Burrel M, Forner A, Sala M, Brunet M, Ayuso C, Castells L, Montañá X, Llovet JM, Bruix J.

Background/Aims:

This study assesses the safety, pharmacokinetics and efficacy of transarterial chemoembolization using drug eluting beads (DEB), an embolizing device that slowly releases chemotherapy to decrease systemic toxicity.

Results:
DEB-TACE was well tolerated with an acceptable safety profile. Two cases developed liver abscess, one leading to death. Response rate was 75% (66.6% on intention-to-treat). After a median follow-up of 27.6 months, 1- and 2-year survival is 92.5% and 88.9%, respectively.

Conclusions:
Chemoembolization using DEBs is an effective procedure with a favorable pharmacokinetic profile.

Anticancer Res. 2006 Sep-Oct;26(5B):3793-5.

Trans-arterial chemoembolization (TACE) of liver metastases from colorectal cancer using irinotecan-eluting beads: preliminary results.
Aliberti C, Tilli M, Benea G, Fiorentini G.

Purpose:
The purpose of the study was to evalutate the feasibility of irinotecan drug-eluting beads (DC Bead) administered as trans-arterial chemoembolization (TACE) in patients with liver metastases from colorectal cancer (CRC).

Results:
TACE with irinotecan eluting beads was found to be feasible and well-tolerated. Right upper quadrant pain (RUQP) lasting 4 days (range 2-7) was reported by all the patients. After 30 days, a reduction >50% of CEA levels and of the lesional contrast enhancement was observed in all the patients.

Conclusion:

Irinotecan drug-eluting beads administered as TACE were shown to be active and safe in patients with liver metastases from CRC.

Cardiovascular Interventional Radiology 2010 Feb; 33(1):41-52.

Prospective randomized study of doxorubicin-eluting-bead embolization in the treatment of hepatocellular carcinoma: results of the PRECISION V study.

Lammer J, Malagari K, Vogl T, Pilleul F, Denys A, Watkinson A, Pitton M, Sergent G, Pfammatter T, Terraz S, Benhamou Y, Avajon Y, Gruenberger T, Pomoni M,Langenberger H, Schuchmann M, Dumortier J, Mueller C, Chevallier P, Lencioni R

Transcatheter arterial chemoembolization (TACE) offers a survival benefit to patients with intermediate hepatocellular carcinoma (HCC). A widely accepted TACE regimen includes administration of doxorubicin-oil emulsion followed by gelatine sponge-conventional TACE. Recently, a drug-eluting bead (DC Bead) has been developed to enhance tumor drug delivery and reduce systemic availability. This randomized trial compares conventional TACE (cTACE) with TACE with DC Bead for the treatment of cirrhotic patients with HCC. Two hundred twelve patients with Child-Pugh A/B cirrhosis and large and/or multinodular, unresectable, N0, M0 HCCs were randomized to receive TACE with DC Bead loaded with doxorubicin or cTACE with doxorubicin. Randomization was stratified according to Child-Pugh status (A/B), performance

status (ECOG 0/1), bilobar disease (yes/no), and prior curative treatment (yes/no). The primary endpoint was tumor response (EASL) at 6 months following independent, blinded review of MRI studies. The drug-eluting bead group showed higher rates of complete response, objective response, and disease control compared with the cTACE group (27% vs. 22%, 52% vs. 44%, and 63% vs. 52%, respectively). The hypothesis of superiority was not met (one-sided P = 0.11). However, patients with Child-Pugh B, ECOG 1, bilobar disease, and recurrent disease showed a significant increase in objective response (P = 0.038) compared to cTACE. DC Bead was associated with improved tolerability, with a significant reduction in serious liver toxicity (P < 0.001) and a significantly lower rate of doxorubicin-related side effects (P = 0.0001). TACE with DC Bead and doxorubicin is safe and effective in the treatment of HCC and offers a benefit to patients with more advanced disease.

Journal of Hepatology. 2012 Dec;57(6):1244-50.

Comparative study between doxorubicin-eluting beads and conventional transarterial Chemoembolisation for treatment of hepatocellular carcinoma.

Song MJ, Chun HJ, Song do S, Kim HY, Yoo SH, Park CH, Bae SH, Choi JY, Chang UI, Yang JM, Lee HG, Yoon SK.

Aims :

Transarterial chemoembolization (TACE) is a widely used treatment for hepatocellular carcinoma. In order to maximize its therapeutic efficacy, doxorubicin-

loaded drug-eluting beads have been developed to deliver higher doses of the chemotherapeutic agent and to prolong contact time with the tumor. The purpose of this study was to evaluate the efficacy and safety of drug-eluting bead (DC bead®) TACE in comparison with conventional TACE (cTACE).

Methods:

A total of 129 patients who underwent TACE between August 2008 and February 2011 were enrolled. We compared HCC patients who underwent TACE with DC bead® (n=60) to controls who received cTACE (n=69). The primary end points were treatment response and treatment-related adverse events. The secondary end point was time to progression.

Results:

The treatment response in the DC bead® group was significantly higher than that of the cTACE group ($p<0.001$). The time to progression was significantly better in the DC bead® group than in the cTACE group (11.7 and 7.6months, respectively, $p=0.018$). Subgroup analysis showed that in intermediate-stage HCC, DC bead® treatment resulted in a significantly better treatment response and longer time to progression than cTACE ($p<0.001$ and 0.038, respectively). However, there was no statistically significant difference in liver toxicity between the DC bead® and cTACE group ($p>0.05$).

Conclusions:

TACE with DC bead® showed better treatment response and delayed tumor progression compared

with cTACE. There was no significant difference in hepatic treatment-related toxicities. DC bead® TACE thus appears to be a feasible and promising approach to the treatment of HCC.

Hepatogastroenterology. 2012 Jan-Feb ; 59(113):255-60.

Safety and efficacy of trans arterial Chemoembolisation with drug-eluting beads in hepatocellular cancer: a systematic review.

Martin R, Geller D, Espat J, Kooby D, Sellars M, Goldstein R, Imagawa D, Scoggins C.

Aim :

The aim of this review was to compare current conventional TACE to the drug eluting beads loaded with doxorubicin (DEBDOX) device in the treatment of HCC.

Method:

A recent hepatocellular consensus discussion was convened to review all recent and past literature in the use of hepatic directed therapies to compare the safety, efficacy and overall survival of the available hepatic directed therapies in the management of hepatocellular cancer. A review of all publications in peer review journals in the English Language from 1995 to 2007 was performed.

Results:

The DEBDOX are an effective therapy with a favorable pharmacokinetic profile with significantly less systemic

doxorubicin exposure when compared to conventional TACE. The DEBDOX had a significant ($p<0.05$) advantage in objective response in the more advanced patients (defined as Child-Pugh B, ECOG 1, recurrent disease and bilobar disease; $p=0.038$) and overall disease control in the more advanced patients ($p=0.026$). The DEBDOX Bead was also found to have a highly significant ($p<0.01$) advantage in the reduction of doxorubicin associated side effects ($p=0.0001$) in all patients.

Conclusions:

The current collective data on the use of DEBDOX Bead in HCC patients provides sufficient evidence to support its use as a safe and effective chemo-embolic treatment in intermediate HCC patients. There is growing evidence to support the its use is superior to conventional doxorubicin TACE.

Cardiovasc Intervent Radiol (2012) 35:1119–1128

Chemoembolization With Doxorubicin-Eluting Beads for Unresectable Hepatocellular Carcinoma: Five-Year Survival Analysis.

Katerina Malagari, Mary Pomoni, Hippocrates Moschouris, Evanthia Bouma, John Koskinas, Aspasia Stefaniotou et al.

Purpose :

The purpose of this study was to report on the 5-year survival of hepatocellular carcinoma (HCC) patients treated with DC Bead loaded with doxorubicin (DEBDOX) in a scheduled scheme in up to three treatments and thereafter on demand.

Methods :

173 HCC patients not suitable for curable treatments were prospectively enrolled (mean age 70.4 ± 7.4 years). Child-Pugh (Child) class was A/B (102/71 [59/41 %]), Okuda stage was 0/1/2 (91/61/19 [53.2/35.7/11.1 %]), and mean lesion diameter was 7.6 ± 2.1 cm. Lesion morphology was one dominant B5 cm (22 %), one dominant [5 cm (41.6 %), multifocal B5 (26%), and multifocal[5 (10.4 %).

Results :

Overall survival at 1, 2, 3, 4, and 5 years was 93.6, 83.8, 62, 41.04, and 22.5 %, with higher rates achieved in Child class A compared with Child class B patients (95, 88.2, 61.7, 45, and 29.4 % vs. 91.5, 75, 50.7, 35.2, and 12.8 %). Mean overall survival was 43.8 months (range 1.2–64.8). Cumulative survival was better for Child class A compared with Child class B patients ($p = 0.029$). For patients with dominant lesions B5 cm 1-, 2-, 3-, 4-, and 5-year survival rates were 100, 95.2, 71.4, 66.6, and 47.6 % for Child class A and 94.1, 88.2, 58.8, 41.2, 29.4, and 23.5 % for Child class B patients. Regarding DEB-DOX treatment, multivariate analysis identified number of lesions ($p = 0.033$), lesion vascularity (p\0.0001), initially achieved complete response (p\0.0001), and objective response ($p = 0.046$) as significant and independent determinants of 5-year survival.

Conclusion

DEB-DOX results, with high rates of 5-year survival for patients, not amenable to curative treatments.

Number of lesions, lesion vascularity, and local response were significant independent determinants of 5-year survival.

Journal of Vascular Interventional Radiology 2013; 24:307–315

Safety and Efficacy of Doxorubicin Drug-eluting Bead Transarterial Chemoembolization in Patients with Advanced Hepatocellular Carcinoma.

Hasmukh J. Prajapati, Renumathy Dhanasekaran, Bassel F. El-Rayes, John S. Kauh, Shishir K. Maithel, Zhengjia Chen, Hyun S. Kim.

Purpose :

To investigate the safety and efficacy of transarterial chemoembolization using doxorubicin drug-eluting beads (DEBs) in patients with Barcelona Clinic Liver Cancer (BCLC) C stage hepatocellular carcinoma (HCC).

Methods :

Consecutive patients with initial staging of BCLC C HCC who received DEB transarterial chemoembolization over the last 5 years were studied. The study included 121 patients (mean age, 61.2 years old). Adverse events (AEs) after DEB transarterial chemoembolization were studied in detail and were recorded as per the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 criteria. Survivals were analyzed according to parameters from the time of first DEB transarterial chemoembolization. Kaplan-Meier method by log-rank

test and Cox proportional hazard model were used for survival analysis.

Results:

AEs occurred in 30.2% of patients. No AEs were greater than Common Terminology Criteria for Adverse Events grade III. Grade I and II AEs included nausea and vomiting in 7.8% of patients and abdominal pain in 23.8% of patients. Grade III AEs were noted in 1.06% of patients. There were no gastrointestinal or hepatic complications. There were no deaths within 30 days after DEB transarterial chemoembolization. The overall median survival was 13.5 months. Among the Child-Pugh class A patients, those without PVT and metastasis (28.9%) had better survival when treated with DEB transarterial chemoembolization than those with PVT and metastases (9.9%) (18.8 mo versus 4.4 mo, P = .001). Ascites, performance status, Okuda stage HCC, serum alpha fetoprotein levels, and etiologic factor for chronic liver disease predicted survival.

Conclusions:

DEB transarterial chemoembolization appears to be a safe and effective treatment option for patients with BCLC C HCC. Patients with Child-Pugh class A without PVT and metastasis benefited most from DEB transarterial chemoembolization.

Anticancer Res. 2012 Apr;32(4):1387-95.

Intra-arterial infusion of irinotecan-loaded drug-eluting beads (DEBIRI) versus intravenous therapy (FOLFIRI) for hepatic metastases from

colorectal cancer: final results of a phase III study.

Fiorentini G, Aliberti C, Tilli M, Mulazzani L, Graziano F, Giordani P, Mambrini A, Montagnani F, Alessandroni P, Catalano V, Coschiera P.

Background:

Metastases to the liver receive most of their blood supply from the arterial route, therefore for patients with hepatic metastases from large bowel cancer, hepatic arterial infusion adopting drug-eluting beads preloaded with irinotecan (DEBIRI) may offer a chance of cure.

Methods:

In a multi-institutional study, 74 patients were randomly assigned to receive DEBIRI (36) versus systemic irinotecan, fluorouracil and leucovorin (FOLFIRI, 38). The primary end-point was survival; secondary end points were response, recurrence, toxicity, quality of life, cost and influence of molecular markers.

Results:

At 50 months, overall survival was significantly longer for patients treated with DEBIRI than for those treated with FOLFIRI (p=0.031, log-rank). Median survival was 22 (95% Confidence Interval CI=21-23) months, for DEBIRI and 15 (95% CI=12-18) months for FOLFIRI. Progression-free survival was 7 (95% CI=3-11) months in the DEBIRI group compared to 4 (95% CI=3-5) months in the FOLFIRI group and the difference between groups was statistically significant (p=0.006,

log-rank). Extra hepatic progression had occurred in all patients by the end of the study, at a median time of 13 (95% CI=10-16) months in the DEBIRI group compared to 9 (95% CI 5-13) months in the FOLFIRI group. A statistically significant difference between groups was not observed (p=0.064, log-rank).The median time for duration of improvement to quality of life was 8 (95% CI=3-13) months in the DEBIRI group and 3 (95% CI=2-4) months in the FOLFIRI group. The difference in duration of improvement was statistically significant (p=0.00002, log-rank).

Conclusions:

This study showed a statistically significant difference between DEBIRI and FOLFIRI for overall survival (7 months), progression-free survival (3 months) and quality of life (5 months). In addition, a clinically significant improvement in time to extra hepatic progression (4 months) was observed for DEBIRI, a reversal of the expectation for a regional treatment. This suggests a benefit of DEBIRI treatment over standard chemotherapy and serves to establish the expected difference between these two treatment options for planning future large randomized studies.

Use of drug eluting beads appears to be safe and effective. Favorable pharmacokinetic profile and tumor response makes this therapy attractive and promising over conventional TACE. Early results shows DEB TACE to be a safe and effective treatment option for patients with BCLC C HCC

Response evaluation

J Comput Assist Tomogr. 2006 Jul-Aug;30(4):578-82.

Completeness of treatment in hepatocellular carcinomas treated with image guided tumor therapies: Evaluation of positive predictive value of contrast enhanced CT with histopathologic correlation in the explanted liver specimen.

Kim YS, Rhim H, Lim HK, Park CK, Lee WJ, Do YS, Cho JW.

Objective:

To evaluate the positive predictive value of contrast-enhanced multiphase computed tomography (CT) in determining the completeness of treatment, after radiofrequency (RF) ablation and/or transcatheter arterial chemoembolization, based on histopathologic correlation in the explanted liver specimen.

Results:

The last CT examinations had been obtained 1-37 days before surgery. The overall necrosis rate of HCC for both RF ablation and transcatheter arterial chemoembolization on microscopic examination was 92.9% +/- 12.3%. The positive predictive value of contrast-enhanced CT in determining completeness of treatment was 69.0% (20/29). The tumor necrosis rate for the RF ablation-only group (n = 12) was 91.5% +/- 15.2% with a positive predictive value of 58.3% (7/12) and that of the transcatheter arterial chemoembolization-only group (n = 11) was 91.4% +/

- 19.2% with a positive predictive value of 72.7% (8/11).

Conclusions:

Study results suggest that contrast-enhanced CT is limited in accurately determining the completeness of treatment after image-guided tumor ablation for HCC.

J Vasc Interv Radiol. 2006 Mar;17(3):505-12.

The role of functional MR imaging in the assessment of tumor response after Chemoembolisation in patients with hepatocellular carcinoma.

Kamel IR, Bluemke DA, Eng J, Liapi E, Messersmith W, Reyes DK, Geschwind JF.

Purpose:

To assess treatment response of hepatocellular carcinoma (HCC) after transarterial Chemoembolisation (TACE) with use of diffusion and dynamic contrast medium-enhanced magnetic resonance (MR) imaging.

Results:

The study included 38 lesions with a mean diameter of 8.0 cm. Mean reduction in tumor diameter was 8 mm after treatment (t test; P = .0005), which did not fulfill Response Evaluation Criteria in Solid Tumors for complete or partial response. Reduction in tumor enhancement in the arterial (30%) and venous (47%) phases was statistically significant (signed-rank test; P = .0003 and P < 0.00005, respectively). Tumor ADC value increased from 0.0015 mm(2)/sec to 0.0018 mm(2)/sec after treatment (t test; P = .026), whereas

the ADC values for the liver, spleen, and muscle remained unchanged. Median patient survival was 19 months.

Conclusions:

After TACE, tumors demonstrated decreased size and enhancement with increases in ADC values. In this cohort, diffusion and dynamic contrast medium-enhanced MR imaging parameters were significantly altered after TACE, and these could be useful tools in the assessment of tumor response.

Multiphase CT is commonly used for response evaluation following Chemoembolisation or RFA but has limitations in predicting completeness of ablation. MRI with diffusion and spectroscopy appears more objective.

Abdominal Imaging. 2010 Aug ; 35(4):447-53.

Evaluation of post treatment response of hepatocellular carcinoma: comparison of ultrasonography with second-generation ultrasound contrast agent and MDCT.

Salvaggio G, Campisi A, Lo Greco V, Cannella I, Meloni MF, Caruso G.

Authors evaluated the ability of one-month follow-up contrast-enhanced ultrasound (CEUS) with second-generation contrast agent in monitoring radio frequency ablation (RFA) and transcatheter arterial chemoembolization (TACE) treatments of hepatocellular carcinoma (HCC). One-hundred forty-eight HCCs were studied using CEUS: 110 nodules

were treated with RFA [41/110 RFA were performed using a pretreatment and an immediate postablation evaluation using CEUS (group 1); 69/110 using only US guidance (group 2)] and 38 nodules treated with TACE. For statistical analysis, McNemar test was used. Overall complete response was observed in 107/148 nodules (92/110 treated with RFA and 15/38 with TACE). A better rate of complete response was found in group 1 compared to group 2 (92.7% vs. 78.3%). In RFA treatment, CEUS showed a sensitivity of 83.3% and a specificity of 100% (diagnostic accuracy of 97%) using MDCT as reference standard with no statistical difference ($p > 0.05$). CEUS detected all cases of incomplete response in HCC treated with TACE using angiography as reference standard (diagnostic accuracy 100%). We recommend assessing residual intratumoral flow on CEUS during RFA procedure to determine the necessity of immediate additional treatment. In case of positive CEUS results, HCC treated with TACE should be considered still viable.

Transarterial Radioembolzation (TARE) :

TARE is an endovascular therapy wherein a tumoricidal dose of radioactive isotope Yttrium 90 (Y-90) is delivered selectively to the tumour the via transarterial route. The preferential deposition of microspheres within the tumor allows intratumoral radiation dose of 100-150Gy to be achieved with reduced risk of radiation induced liver damage. Two commercially available microspheres have either resin or glass microspheres loaded with yttrium-90. Y90 is a high-energy radiation source which is a pure beta emitter with a half life of

2.67 days (64.2 hours) with short tissue penetration of 2.5 mm.

Indications / Applications :

1. The following candidates are selected for Y90 therapy for HCC.
   - Patients within transplant criteria: As a bridge to transplant.
   - Patients beyond transplant criteria: Downstage to transplant or resection.
   - Radioembolisation for patients with advanced disease: Palliative treatment to improve quality of life.
2. Loco regional disease control in patient with colorectal metastasis.
3. Loco regional disease control in patient with Neuroendocrine liver metastasis.
4. Loco regional disease control in patient with intrahepatic cholangiocarcinoma.

Transarterial Radioembolisation for Hepatocellular Carcinoma

J Vasc Interv Radiol. 2005 Dec;16(12):1627-39.

Treatment of unresectable hepatocellular carcinoma with use of 90Y microspheres (TheraSphere): safety, tumor response, and survival.

Salem R, Lewandowski RJ, Atassi B, Gordon SC, Gates VL, Barakat O, Sergie Z, Wong CY, Thurston KG.

Purpose:

To present safety and efficacy results obtained in treatment of a cohort of patients with unresectable hepatocellular carcinoma (HCC) with use of 90Y microspheres.

Methods:

Forty-three consecutive patients with HCC were treated with 90Y microspheres over a 4-year period. Patients were treated by liver segment or lobe on one or more occasions based on tumor distribution, liver function, and vascular flow dynamics. Patients were followed for adverse events, objective tumor response, and survival. Patients were stratified into three risk groups according to method of treatment and risk stratification (group 0, segmental; group 1, lobar low-risk; group 2, lobar high-risk) and Okuda and Child-Pugh scoring systems.

Results:

Based on follow-up data from 43 treated patients, 20 patients (47%) had an objective tumor response based on percent reduction in tumor size and 34 patients (79%) had a tumor response when percent reduction and/or tumor necrosis were used as a composite measure of tumor response. There was no statistical difference among the three risk groups with respect to tumor response. Survival times from date of diagnosis were different among the risk groups ($P < .0001$). Median survival times were 46.5 months, 16.9 months, and 11.1 months for groups 0, 1, and 2, respectively. Median survival times of 24.4 months and 12.5 months

by Okuda scores of I and II, respectively, were achieved (mean, 25.8 months vs 13.1). Patients had median survival times of 20.5 months and 13.8 months according to Child class A and class B/C disease, respectively (mean, 22.7 months vs 13.6 months). Patients classified as having diffuse disease exhibited decreased survival and reduced tumor response. There were no life-threatening adverse events related to treatment.

Conclusions:

Use of 90Y microspheres (TheraSpheres) provides a safe and effective method of treatment for a broad spectrum of patients presenting with unresectable HCC. Further investigation is warranted.

Transarterial Radioembolisation for colorectal liver metastasis

Cardiovasc Intervent Radiol. 2009 Nov;32(6):1179-86.

Selective internal radiation therapy with SIR-spheres for the treatment of unresectable colorectal hepatic metastases.

Cianni R, Urigo C, Notarianni E, Saltarelli A, Salvatori R, Pasqualini V, Dornbusch T, Cortesi E.

Purpose :

To evaluate the effectiveness of colorectal cancer (CRC) liver metastasis radioembolization with yttrium-90 (Y90), assessing toxicity and survival rates in patients with no response to chemotherapy through our 3-year

experience. From February 2005 to January 2008, we treated 41 patients affected by CRC from a cohort of selective internal radiation therapy patients treated at our institution. All patients examined showed disease progression and arrived for our observation with an abdominal CT, a body PET, and a hepatic angiography followed by gastroduodenal artery coiling previously performed by us. We excluded patients with a bilirubin level>1.8 mg/dl and pulmonary shunt>20% but not patients with minor extrahepatic metastases. On treatment day, under fluoroscopic guidance, we implanted a dose of Y90 microspheres calculated on the basis of liver tumoral involvement and the body surface area formula. All patients were discharged the day after treatment. We obtained, according to Response Evaluation Criteria on Solid Tumors, a complete response in 2 patients, a partial response in 17 patients, stable disease in 14 patients, and progressive disease in 8 patients. In all cases, we obtained a carcinoembryonic antigen level decrease, especially in the week 8 evaluation. Technical success rate was 98% and technical effectiveness estimated at 3 months after treatment was 80.5%. Side effects graded by Common Terminology Criteria on Adverse Events were represented by one grade 4 hepatic failure, two grade 2 gastritis, and one grade 2 cholecystitis. The median survival and the progression-free survival calculated by Kaplan-Meier analysis were 354 and 279 days, respectively. In conclusion, according to our 3-year experience, Y90 SIR-Spheres radioembolization is a feasible and safe method to treat CRC liver metastases, with an acceptable level of complications and a good response rate.

J Vasc Interv Radiol 2008; 19:1187–1195

Hepatic Yttrium-90 Radioembolization of Chemotherapy-refractory Colorectal Cancer Liver Metastases

Tobias F. Jakobs, Ralf-Thorsten Hoffmann, Kristina Dehm, Christoph Trumm et al.

Purpose:

To present data for radioembolization with yttrium-90 (90Y) resin microspheres in patients with colorectal cancer liver metastases in whom currently available therapies had failed.

Methods:

Retrospective review was conducted of case files of patients with colorectal cancer liver metastases in whom chemotherapy had failed, prompting hepatic 90Y radioembolization administered as a single-session, whole-liver treatment. Imaging and laboratory follow-up results were available for 36 patients. Response and toxicity were assessed by computed tomography/magnetic resonance imaging with the Response Evaluation Criteria in Solid Tumors and the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 3.0.

Results:

Forty-one patients (mean age, 61 years; 30 men) received hepatic 90Y radioembolization with resin microspheres (mean activity, 1.9 GBq). At a median interval of 2.9 months after radioembolization, partial response, stable disease, and progressive disease were

demonstrated in seven, 25, and four patients, respectively. Median overall survival was 10.5 months, with improved survival for patients with a decrease in carcinoembryonic antigen level (19.1 months vs 5.4 months) and imaging response (29.3 months vs 4.3 months). Except for one instance of treatment associated cholecystitis (grade 4 toxicity) and two gastric ulcers (grade 2 toxicity), no severe toxicities were observed.

Conclusions:

Hepatic 90Y radioembolization can be performed with manageable toxicity in patients with colorectal cancer liver metastases whose disease is refractory to chemotherapy. The antitumoral effect is supported by imaging and tumor marker responses.

Transarterial Radioembolisation for Neuroendocrine liver metastases

Radioembolization of Symptomatic, Unresectable Neuroendocrine Hepatic Metastases Using Yttrium-90 Microspheres

Cardiovasc Intervent Radiol (2012) 35:334–342

Philipp M. Paprottka, Ralf-T. Hoffmann, Alexander Haug , Wieland H. Sommer et al.

Purpose:

To evaluate safety, efficacy, and symptom control of radioembolization in patients with unresectable liver metastases from Neuroendocrine tumors (NETLMs).

Materials and Methods

Forty-two patients (mean age of 62 years) with treatment-refractory NETLMs underwent Radioembolisation using yttrium-90 (90Y) resin microspheres. Posttreatment tumor response was assessed by cross-sectional imaging using the Response Evaluation Criteria in Solid Tumors (RECIST) and tumor-marker levels. Laboratory and clinical toxicities and clinical symptoms were monitored.

Results:

The median activity delivered was 1.63 GBq (range 0.63–2.36). Imaging follow-up using RECIST at 3-month follow-up demonstrated partial response, stable disease, and progressive disease in 22.5, 75.0, and 2.5% of patients, respectively. In 97.5% of patients, the liver lesions appeared hypovascular or partially necrotic. The mean follow-up was 16.2 months with 40 patients (95.2%) remaining alive. The median decrease in tumor-marker levels at 3 months was 54.8% (chromogranin A) and 37.3% (serotonin), respectively. There were no acute or delayed toxicities greater than grade 2 according to Common Terminology Criteria for Adverse Events [CTCAE (v3.0)]. No radiation-induced liver disease was noted. Improvement of clinical symptoms 3 months after treatment was observed in 36 of 38 symptomatic patients.

Conclusion:

Radioembolization with 90Y-microspheres is a safe and effective treatment option in patients with otherwise

treatment-refractory NETLMs. Antitumoral effect is supported by good local tumor control, decreased tumor-marker levels, and improved clinical symptoms. Further investigation is warranted to define the role of radioembolization in the treatment paradigm for NETLMs.

Transarterial Radioembolisation for Intrahepatic Cholangiocarcinoma

Cardiovasc Intervent Radiol (2013) 36:440–448

Yttrium-90 Radioembolization for Unresectable Standard- chemorefractory Intrahepatic Cholangiocarcinoma: Survival, Efûcacy, and Safety Study.

Shoaib Raû, Sarat M. Piduru, Bassel El-Rayes, John S. Kauh, David A. Kooby, Juan M. Sarmiento, Hyun S. Kim

Purpose:

To assess the overall survival, efûcacy, and safety of radioembolization with yttrium-90 (Y90) for unresectable standard chemorefractory intrahepatic cholan- giocarcinoma (ICC).

Methods:

Patients with unresectable standard-chemore- fractory ICC treated with Y90 were studied. Survival was calculated from the date of ûrst Y90 procedure. Tumor response was assessed with the Response Evaluation Cri- teria in Solid Tumors criteria on follow-up computed tomography or magnetic resonance imaging

scans. National Cancer Institute Common Terminology Criteria (NCI CTCAE), version 3, were used for complications. Statistical analysis was performed by the Kaplan–Meier estimator by the log rank test. Results Nineteen patients underwent a total of 24 resin- based Y90 treatments. Median survival from the time of diagnosis and ûrst Y90 procedure was 752 ± 193 [95 % conûdence interval (CI) 374–1130] and 345 ± 128 (95 % CI 95–595) days, respectively. Median survival with Eastern Cooperative Oncology Group (ECOG) performance status 1 (n = 15) and ECOG performance status 2 Purpose To assess the overall survival, efûcacy, and safety of radioembolization with yttrium-90 (Y90) for un- resectable standard-chemorefractory intrahepatic cholan- giocarcinoma (ICC). Methods Patients with unresectable standard-chemore- fractory ICC treated with Y90 were studied. Survival was calculated from the date of ûrst Y90 procedure. Tumor response was assessed with the Response Evaluation Cri- teria in Solid Tumors criteria on follow-up computed tomography or magnetic resonance imaging scans. National Cancer Institute Common Terminology Criteria (NCI CTCAE), version 3, were used for complications. Statistical analysis was performed by the Kaplan–Meier estimator by the log rank test.

Results:

Nineteen patients underwent a total of 24 resin- based Y90 treatments. Median survival from the time of diagnosis and ûrst Y90 procedure was 752 ± 193 [95 % conûdence interval (CI) 374–1130] and 345 ± 128 (95 % CI 95–595) days, respectively. Median survival with

Eastern Cooperative Oncology Group (ECOG) performance status 1 (n = 15) and ECOG performance status 2 (n = 4) was 450 ± 190 (95 % CI 78–822) and 345 ± 227 (95 % CI 0–790) days, respectively (p = .214). Patients with extrahepatic metastasis (n = 11) had a median sur- vival of 404 ± 309 (95 % CI 0–1010) days versus 345 ± 117 (95 % CI 115–575) days for patients without metastasis (n = 8) (p = .491). No mortality was reported within 30 days from ûrst Y90 radioembolization. One patient developed grade 3 thrombocytopenia as assessed by NCI CTCAE. Fatigue and transient abdominal pain were observed in 4 (21 %) and 6 (32 %) patients, respectively.

Conclusion:

Y90 radioembolization is effective for unre- sectable standard-chemorefractory ICC.

Yttrium-90 Radioembolization for Intrahepatic Cholangiocarcinoma: Safety, Response and Survival Analysis

J Vasc Interv Radiol 2013; 24:1227–1234

Samdeep Mouli, Khairuddin Memon, Talia Baker, Al B.Benson,III, Mary F.Mulcahy, Ramona Gupta, Robert K.Ryu, RiadSalem, RobertJ.Lewandowski.

Purpose:

To present data on safety, antitumoral response, and survival following yttrium-90 ((90)Y) radioembolization for patients with unresectable intrahepatic cholangiocarcinoma (ICC).

Methods:

The present study expands on the cohort of 24 patients with ICC described in a pilot study, and includes 46 patients treated with (90)Y radioembolization at a single institution during an 8-year period. Via retrospective review of a prospectively collected database, patients were stratified by performance status, tumor distribution (solitary or multifocal), tumor morphology (infiltrative or peripheral), and presence/absence of portal vein thrombosis. Primary endpoints included biochemical and clinical toxicities, and secondary endpoints included imaging response (World Health Organization [WHO] and European Association for the Study of Liver Disease [EASL] criteria) and survival. Uni-/multivariate analyses were performed.

Results:

Ninety-two treatments were performed, with a mean of two per patient. Fatigue and transient abdominal pain occurred in 25 patients (54%) and 13 patients (28%), respectively. Treatment-related gastroduodenal ulcer developed in one patient (2%). WHO imaging findings included partial response (n = 11; 25%), stable disease (n = 33; 73%), and progressive disease (n = 1; 2%). EASL imaging findings included partial/complete response (n = 33; 73%) and stable disease (n = 12; 27%). Survival varied based on presence of multifocal (5.7 mo vs 14.6 mo), infiltrative (6.1 mo vs 15.6 mo), and bilobar disease (10.9 mo vs 11.7 mo). Disease was converted to resectable status in five patients, who successfully underwent curative (ie, R0) resection.

Conclusions:
Radioembolization with (90)Y is safe and demonstrates antitumoral response and survival benefit in select patients with ICC. Results are most pronounced in patients with solitary tumors, for whom conversion to curative resection is possible.

Complications after Transarterial Radioembolisation

Complications Following Radioembolization with Yttrium-90 Microspheres: A Comprehensive Literature Review

J Vasc Interv Radiol 2009; 20:1121–1130

Ahsun Riaz, Robert J. Lewandowski, Laura M. Kulik, Mary F. Mulcahy, Kent T. Sato, Robert K. Ryu, Reed A. Omary, and Riad Salem

The past decade has seen significant advancement in the locoregional management of liver tumors; novel and promising therapies such as transarterial chemoembolization, radioembolization, and radiofrequency ablation are now available. The development of new techniques and devices has led to the improved safety and efficacy profiles of external-beam radiation. Radioembolization with yttrium-90 (90Y) microspheres has emerged as a safe and efficacious treatment modality for liver malignancies. The mild adverse events and constitutional symptoms after radioembolization rarely require hospitalization. Serious adverse events can be mitigated if proper patients are selected, accepted dosimetry models used, and meticulous technique employed (Table 2). Patients

with poor liver function before treatment are more prone to develop RILD. Derangement in liver function can be prevented by lobar or segmental injection and avoidance of whole-liver treatment (35). Biliary sequelae occur mostly after treatment of secondary tumors (from polychemotherapy) and generally do not lead to clinical consequences that require unplanned intervention. Portal hypertension is an imaging phenomenon that may be seen after treatment to both lobes of the liver. Radiation pneumonitis is rarely seen after radioembolization, but caution should be exercised in patients with increased LSF. GI ulceration caused by radioembolization is a serious complication that may require surgery if refractory to conservative measures. It can be prevented by meticulous mapping during pretreatment angiography and prophylactic coil embolization. Care should be taken regarding the risk of vascular injury in patients receiving chemotherapy. Lymphopenia may occur after radioembolization but has not been shown to lead to clinical sequelae.

Portal Vein Embolization

Percutaneous portal vein embolization has matured into a well validated treatment modality for inducing hypertrophy of the Future Liver Remnant (FLR) in patients with small FLR.

The aim of the procedure is to induce hypertrophy of the non-diseased portion of the liver so that the diseased portion can be safely removed without compromising synthetic liver function. This is achieved by embolizing the portal vein branches in the tumor bearing liver which is to be resected resulting in the

entire portal venous inflow being directed to the FLR, which undergoes hypertrophy under the influence of various trophic factors like Hepatocyte growth factor (HGF) and Insulin. Liver regeneration peaks within first 2 weeks after PVE. Regeneration rates are slower in diabetics and cirrhotics.

1. Future Liver Remnant (FLR): It is the volume of the (non-diseased) remnant liver that remains after resection.
2. Total Liver Volume: Volume of the entire liver measured with CT.
3. Total Estimated Liver Volume (TELV) can be calculated based on the body weight or body mass index.

A ratio of FLR/TELV is calculated.

Patients are selected for PVE based on this ratio as follows:

I. FLR/TELV < 25% for normal liver

II.FLR/TELV < 40% for compromised liver function (Cirrhosis or high dose chemotherapy).

Contraindications:

No absolute contraindications for PVE. PVE is relatively contraindicated in patients with –

1. Uncorrectable coagulopathy
2. Tumor thrombus in portal vein
3. Portal hypertension
4. Distant metastases or other factors which may preclude surgery after PVE.

Post procedure surveillance and timing the resection:

Repeat CT at 2-4 wks to assess FLR hypertrophy.

Annals of Surgery 2008 January ; 247(1):49-57.

***Preoperative portal vein embolization for major liver resection: a metaanalysis*.**

Abulkhir A, Limongelli P, Healey AJ, Damrah O, Tait P, Jackson J, Habib N, Jiao LR.

Purpose:

Preoperative portal vein embolization (PVE) is used clinically to prevent postoperative liver insufficiency. This study examined the impact of portal vein embolization on liver resection.

Method:

A comprehensive Medline search to identify all registered literature in the english language on portal vein embolization. Meta-analysis was performed to assess the result of PVE and its impact on major liver resection.

Result:

A total of 75 publications met the search criteria but only 37 provided data sufficiently enough for analysis involving 1088 patients. The overall morbidity rate for PVE was 2.2% without mortality. Four weeks following PVE, 85% patients underwent the planned hepatectomy (n = 930). Twenty-three patients had transient liver failure following resection after PVE (2.5%) but 7 patients developed acute liver failure and died (0.8%).The reason for nonresection following PVE

(n = 158, 15%) included inadequate hypertrophy of remnant liver (n = 18), severe progression of liver metastasis (n = 43), extrahepatic spread (n = 35), refusal to surgery (n = 1), poor general condition (n = 1), altered treatment to transcatheter artery embolization or chemotherapy (n = 24), complete remission after treatment with 3 cycles of fluoracil and interferon alpha in a patient with hepatocellular carcinoma (n = 1), incomplete pre- or postembolization scanning (n = 8). Of those who underwent laparotomy without resection, (n = 27) reasons included intraoperative finding of peritoneal dissemination (n = 15), portal node metastasis (n = 2), severe invasion of the tumor to the hepatic artery and portal vein (n = 1), and gross tumoral extension precluding curative resection (n = 9).Two techniques were used for portal vein embolization: percutaneous transhepatic portal embolization, (PTPE) and transileocolic portal embolization, (TIPE). The increase in remnant liver volume was much greater in PTPE than TIPE group (11.9% vs. 9.7%; P = 0.00001). However, the proportion of patients who underwent resection following PVE was 97% in TIPE and 88% PTPE, respectively (P = <0.00001). Although there was no significant difference in patients who had major complications post-PVE, the rate for minor complications was significantly higher among patients who had PTPE (53.6% vs. 0%, P = <0.0001).

Conclusions:

PVE is a safe and effective procedure in inducing liver hypertrophy to prevent post resection liver failure due to insufficient liver remnant.

Journal of Gastrointestinal Surgery 2008 January;12(1):123-8. Epub 2007 Oct 9.

Comparison of two methods of future liver remnant volume measurement.

Chun YS, Ribero D, Abdalla EK, Madoff DC, Mortenson MM, Wei SH, Vauthey JN.

Background:

In liver transplantation, a minimum graft to patient body weight (BW) ratio is required for graft survival; in liver resection, total liver volume (TLV) calculated from body surface area (BSA) is used to determine the future liver remnant (FLR) volume needed for safe hepatic resection. These two methods of estimating liver volume have not previously been compared. The purpose of this study was to compare FLR volumes standardized to BW versus BSA and to assess their utility in predicting postoperative hepatic dysfunction after hepatic resection.

Results:

Regression analysis revealed that the FLR/TLV and FLR/BW ratios were highly correlated (Pearson correlation coefficient, 0.98). The area under the ROC curve was 0.85 for FLR/TLV and 0.84 for FLR/BW (95% confidence interval, 0.71-0.97). Sixteen of the 68 patients developed postoperative hepatic dysfunction. The ROC curve analysis yielded a cutoff FLR/BW value of </=0.4, which had a positive predictive value (PPV) of 78% and a negative predictive value (NPV) of 85%. The corresponding FLR/TLV cutoff value of </=20% had a PPV of 80% and a NPV of 86%.

Conclusions:

Based on the strong correlation between the FLR measurements standardized to BW and BSA and their similar ability to predict postoperative hepatic dysfunction, both methods are appropriate for assessing liver volume. In noncirrhotic patients, a FLR/BW ratio of </=0.4 and FLR/TLV of </=20% provide equivalent thresholds for performing safe hepatic resection.

British Journal of Surgery 2007 November ; 94(11):1386-94.

Portal vein embolization before major hepatectomy and its effects on regeneration, resectability and outcome.

Ribero D, Abdalla EK, Madoff DC, Donadon M, Loyer EM, Vauthey JN.

Background:

This study evaluated the safety of portal vein embolization (PVE), its impact on future liver remnant (FLR) volume and regeneration, and subsequent effects on outcome after liver resection.

Methods:

Records of 112 patients were reviewed. Standardized FLR (sFLR) and degree of hypertrophy (DH; difference between the sFLR before and after PVE), complications and outcomes were analysed to determine cut-offs that predict postoperative hepatic dysfunction.

Results:

Ten (8.9 per cent) of 112 patients had PVE-related complications. Postoperative complications occurred

in 34 (44 per cent) of 78 patients who underwent hepatic resection and the 90-day mortality rate was 3 per cent. A sFLR of 20 per cent or less after PVE or DH of not more than 5 per cent (versus sFLR greater than 20 per cent and DH above 5 per cent) had a sensitivity of 80 per cent and a specificity of 94 per cent in predicting hepatic dysfunction. Overall, major and liver-related complications, hepatic dysfunction or insufficiency, hospital stay and 90-day mortality rate were significantly greater in patients with a sFLR of 20 per cent or less or DH of not more than 5 per cent compared with patients with higher values.

Conclusions:

DH contributes prognostic information additional to that gained by volumetric evaluation in patients undergoing PVE.

Radiology 2005; 234(2):625-30.

Preoperative Percutaneous Portal Vein Embolization: Evaluation of Adverse Events in 188 Patients

Donatella R. Di Stefano, Thierry de Baere,, Alban Denys, Antoine Hakime, Gilles, Gorin, Michel Gillet, Jean Saric, Hervé Trillaud, Philippe Petit, Jean- Michel Bartoli, Dominique Elias, and Jean-Robert Delpero.

Purpose:

To retrospectively assess the frequency of adverse events related to percutaneous preoperative portal vein embolization (PPVE).

Results:

Adverse events occurred in 24 (12.8%) of 188 patients, including 12 complications and 12 incidental imaging findings. Complications included thrombosis of the portal vein feeding the future remnant liver (n = 1); migration of emboli in the portal vein feeding the future remnant liver, which necessitated angioplasty (n = 2); hemoperitoneum (n = 1); rupture of a metastasis in the gallbladder (n = 1); transitory hemobilia (n = 1); and transient liver failure (n = 6). Incidental findings were migration of small emboli in nontargeted portal branches (n = 10) and subcapsular hematoma (n = 2). Among the 187 patients in whom PPVE was technically successful, there was a significant difference (P< .001) between the occurrence of liver failure after PPVE in patients with cirrhosis (five of 30) and those without (one of 157). Sixteen liver resections were cancelled due to cancer progression (n = 12), insufficient hypertrophy of the nonembolized liver (n = 3), and complete portal thrombosis (n = 1).

Conclusions:

PPVE is a safe adjuvant technique for hypertrophy of the initially insufficient liver reserve. Post-PPVE transient liver failure is more common in patients with cirrhosis than in those without cirrhosis.

Journal of Vascular and interventional Radiology 2005 Feb;16(2 Pt 1):215-25.

Transhepatic ipsilateral right portal vein embolization extended to segment IV: improving hypertrophy and resection outcomes with spherical particles and coils.

Madoff DC, Abdalla EK, Gupta S, Wu TT, Morris JS, Denys A, Wallace MJ, Morello FA Jr, Ahrar K, Murthy R, Lunagomez S, Hicks ME, Vauthey JN.

Purpose:

To analyze outcomes after right portal vein embolization extended to segment IV (right PVE + IV) before extended right hepatectomy, including liver hypertrophy, resection rates, and complications after embolization and resection, and to assess differences in outcomes with two different particulate embolic agents.

Methods:

Between 1998 and 2004, transhepatic ipsilateral right PVE + IV with particles and coils was performed in 44 patients with malignant hepatobiliary disease, including metastases (n = 24), biliary cancer (n = 14), and hepatocellular carcinoma (n = 6). Right PVE + IV was considered if the future liver remnant (FLR; segments II/III with or without I) was less than 25% of the total estimated liver volume (TELV). Tris-acryl microspheres (100- 700 microm; n = 21) or polyvinyl alcohol (PVA) particles (355-1,000 microm; n = 23) were administered in a stepwise fashion. Smaller particles were used to occlude distal branches, followed by larger particles to occlude proximal branches until near-complete stasis. Coils were then placed in secondary portal branches. Computed tomographic volumetry was performed before and 3-4 weeks after right PVE + IV to assess FLR hypertrophy. Liver volumes and postembolization and postoperative outcomes were measured.

Results:

After right PVE + IV with PVA particles, FLR volume increased 45.5% +/- 40.9% and FLR/TELV ratio increased 6.9% +/- 5.6%. After right PVE + IV with tris-acryl microspheres, FLR volume increased 69.0% +/- 30.7% and FLR/TELV ratio increased 9.7% +/- 3.3%. Differences in FLR volume (P = .0011), FLR/TELV ratio (P = .027), and resection rates (P = .02) were statistically significant. Seventy-one percent of patients underwent extended right hepatectomy (86% after receiving tris-acryl microspheres, 57% after receiving PVA). Thirteen patients (29%) did not undergo resection (extra hepatic spread [n = 9], inadequate hypertrophy [n = 3], other reasons [n = 1]). No patient developed postembolization syndrome or progressive liver insufficiency after embolization or resection. One death after resection occurred as a result of sepsis and hemorrhage. Median hospital stays were 1 day after right PVE + IV and 7 days after resection.

Conclusions:

Transhepatic ipsilateral right PVE + IV with use of particles and coils is a safe, effective method for inducing contralateral hypertrophy before extended right hepatectomy. Embolization with small spherical particles provides improved hypertrophy and resection rates compared with larger, nonspherical particles.

Annals of Surgery 2006 March ; 243 (3) : 364-72.

Two hundred forty consecutive portal vein embolization before extended hepatectomy for biliary cancer: surgical outcome and long-term follow-up.

Nagino M, Kamiya J, Nishio H, Ebata T, Arai T, Nimura Y

Objective:

To assess clinical benefit of portal vein embolization (PVE) before extended, complex hepatectomy for biliary cancer.

Background Data:

Many investigators have addressed clinical utility of PVE before simple hepatectomy for metastatic liver cancer or hepatocellular carcinoma, but few have reported PVE before hepatectomy for biliary cancer due to the limited number of surgical cases.

Conclusions:

PVE has the potential benefit for patients with advanced biliary cancer who are to undergo extended, complex hepatectomy. Along with the use of PVE, further

Improvements in surgical techniques and refinements in perioperative management are necessary to make difficult hepatobiliary resections safer.

World J Gastroenterol 2012 May 21; 18(19): 2371-2376

Comparison of percutaneous transhepatic portal vein embolization and unilateral portal vein ligation

Hiroya Iida, Tsukasa Aihara, Shinichi Ikuta, Hidenori Yoshie, Naoki Yamanaka

Aim:

To compare the effect of percutaneous transhepatic portal vein embolization (PTPE) and unilateral portal

vein ligation (PVL) on hepatic hemodynamic and right hepatic lobe (RHL) atrophy.

Methods:

Between March 2005 and March 2009, 13 cases were selected for PTPE (n = 9) and PVL (n= 4) in the RHL. The PTPE group included hilar bile duct carcinoma (n = 2), intrahepatic cholangiocarcinoma (n = 2), hepatocellular carcinoma (n = 2) and liver metastasis (n = 3). The PVL group included hepatocellular carcinoma (n = 2) and liver metastasis (n = 2). In addition, observation of postoperative hepatic hemodynamics obtained from computed tomography and Doppler ultrasonography was compared between the two groups.

Results:

Mean ages in the two groups were 58.9 ± 2.9 years (PVL group) *vs* 69.7 ± 3.2 years (PTPE group), which was a significant difference (P = 0.0002). Among the indicators of liver function, including serum albumin, serum bilirubin, aspartate aminotransferase, alanine aminotransferase, platelets and indocyanine green retention rate at 15 min, no significant differences were observed between the two groups. Preoperative RHL volumes in the PTPE and PVL groups were estimated to be 804.9 ± 181.1 mL and 813.3 ± 129.7 mL, respectively, with volume rates of 68.9% ± 2.8% and 69.2% ± 4.2%, respectively. There were no significant differences in RHL volumes (P = 0.83) and RHL volume rates (P = 0.94), respectively. At 1 mo after PTPE or PVL, postoperative RHL volumes in the PTPE and PVL

groups were estimated to be 638.4 ± 153.6 mL and 749.8 ± 121.9 mL, respectively, with no significant difference (P = 0.14). Postoperative RHL volume rates in the PTPE and PVL groups were estimated to be 54.6% ± 4.2% and 63.7% ± 3.9%, respectively, which was a significant difference (P = 0.0056). At 1 mo after the operation, the liver volume atrophy rate was 14.3% ± 2.3% in the PTPE group and 5.4% ± 1.6% in the PVL group, which was a significant difference (P = 0.0061).

Conclusions:

PTPE is a more effective procedure than PVL because PTPE is able to occlude completely the portal branch throughout the right peripheral vein.

Br J Radiol. 2006 Jun;79(942):473-8.

Portal vein embolisation prior to hepatic resection for colorectal liver metastases and the effects of periprocedure chemotherapy.

Beal IK, Anthony S, Papadopoulou A, Hutchins R, Fusai G, Begent R, Davies N, Tibballs J, Davidson B.

Portal vein embolisation (PVE) is an effective method of increasing future liver remnant (FLR) but may stimulate tumour growth. The effect of periprocedure chemotherapy has not been established. 15 consecutive patients underwent PVE prior to hepatic resection for colorectal liver metastases with a FLR <30% of tumour-free liver (TFL). Liver and tumour volumes pre-PVE and 6 weeks post- PVE were calculated by CT or MRI volumetry and correlated with the periprocedure

chemotherapy regimen. PVE increased the FLR from 18+/-5% of TFL to 27+/-8% post-PVE ($p<0.01$). Post-PVE chemotherapy did not prevent hypertrophy of the FLR but the volume increase with chemotherapy (median 89 ml, range 7-149 ml) was significantly reduced (median 135 ml, range 110-254 ml without chemotherapy) ($p = 0.016$). Tumour volume (TV) decreased in those receiving post-PVE chemotherapy (median TV decrease 8 ml, range -77 ml to +450 ml) and increased without chemotherapy (median TV increase 39 ml, range -58 ml to +239 ml). Of the 15 patients, eight underwent resection; four were not resected due to disease progression and three due to insufficient hypertrophy of the FLR. PVE increased the FLR by an average of 9% allowing resection in 50% of patients. Periprocedure chemotherapy did not prevent but did reduce hypertrophy. A trend towards tumor regression was observed.

Portal vein embolization is a safe and effective procedure for inducing hypertrophy of the future liver remnant (FLR) in patients with a suboptimal FLR volume. Ipsilateral approach is safer as it avoids access through the FLR. PVE can be used in patients with HCC, metastases and biliary cancer. PVE widens the safety margin for liver resection. Shortening the interval and using interval chemotherapy between PVE and resection is advisable to reduce the incidence of disease progression.

Imaging of Renal Neoplasms:

Renal cell Carcinoma (RCC) is the third most common and most lethal of all genitourinary malignancies. It accounts for 1.5% of all malignancies in India. Renal masses are asymptomatic and non-palpable until late stage of disease. The peak incidence of RCC is in 7th decade, and there is a male preponderance in the ratio to females (1.5: 1). RCCs are extremely uncommon in children and constitute 2.3 to 6.6 % of all childhood renal tumors. The mean age at diagnosis in children is 8 to 9 years with equal incidence in both sexes. RCCs in children are more likely to be of papillary histology, often are locally advanced, have high grade features and can have unfavorable histological variants; hence aggressive surgery is recommended for RCCs in children and young adults. *Risk factors include increased age; male sex; smoking; cadmium, benzene, trichloroethylene, and asbestos exposure; excessive weight; chronic dialysis use; and several genetic syndromes (familial RCC, hereditary papillary RCC, von Hippel-Lindau syndrome, and tuberous sclerosis). The

following imaging modalities may be used for detection and characterization of renal masses; ultrasound (US), computed tomography (CT), or magnetic resonance imaging.

***http://www.tripdatabase.com/doc/815035-Renal-Cell-Carcinoma**

The imaging modality of choice for evaluation of Renal cell carcinoma is computed tomography with a dedicated renal protocol that allows detection, staging (extent and morphology of the lesion, the nodal status, evaluation of the extrarenal spread, evaluation of renal vein and inferior vena cava) and surgical planning. It also provides information of the contralateral kidney and metastases in the abdominal region and CT of the thorax is used for pulmonary metastatic evaluation (***level of evidence 3**). Imaging is used to classify renal lesions as solid or cystic. For solid renal mass, the most important criteria in differentiating a malignant lesion is the presence of enhancement (**level of evidence 3**). If a solitary renal mass enhances, the degree of confidence in diagnosis of RCC is high; however other enhancing renal masses such as metastasis, oncocytoma, non-fat containing angiomyolipoma and lymphoma need to be differentiated from RCC. The cystic renal lesions are assessed using Bosniak classification, this classification categorizes renal cystic lesion into five categories based on imaging appearances to predict risk of malignancy. For tumor thrombus evaluation; either CT scan or Doppler US (***level of evidence 3**) can be used. A majority of renal masses can be diagnosed accurately

with imaging. In addition, CT scan provides information on renal function and condition of the adrenal gland.

CT is widely used and standard imaging modality for evaluation of renal masses; with almost universal availability of **M**ulti **D**etector row **C**omputed **T**omography (MDCT), **multiphase imaging is a must for optimal evaluation of renal masses**. Prior to contrast enhanced multiphase CT, an unenhanced CT scan is obtained, which shows calcific foci if present, and serves as a baseline for measurement of enhancement and should include also the entire liver. The imaging should be performed with a slice thickness of 2.5 or 3.0 mm. The multiphase CT includes an arterial phase 20 to 25 seconds (secs) after start of injection of contrast and is useful for the derivation of angiographic images, the slice thickness for arterial phase must be 1.25 or 1.5 mm and rate of injection of 3 to 4 cc per second, the cortico-medullary phase/ portal venous phase is obtained approximately 60 to 70 secs after start of injection useful for staging information, and it also optimally depicts renal vein and the liver also can be evaluated; the nephrographic phase aids in the delineation of renal masses and is obtained approximately at 80- 90 seconds after start of contrast injection; the final phase is the excretory phase which helps in evaluation of the relationship of renal mass to the collecting system and aids in surgical planning. The imaging parameters should be the same for all phases. There can be false positive results because of beam hardening artifact or due to reconstruction algorithm used which can lead to pseudo-enhancement. False negative results can happen if

lesions are too small to characterize, if attenuation measurements are improperly done and if septae are not adequately evaluated in cystic lesions.

For the evaluation of small renal masses (measuring </= 3.0 cm in diameter), the relative sensitivity of the various imaging modalities, reported in the literature is 67% for excretory urography, 79% for ultrasonography and 94% for conventional CT scan. Excretory urography in addition lacks specificity for characterization of renal masses. For evaluation, of cystic renal lesions; ultrasonography is perhaps the best modality.

Magnetic **R**esonance **I**maging (MRI) is used as a problem solving modality. If CT scan findings are indeterminate and when use of iodinated contrast is precluded, due to history of allergy or prior reaction to iodinated contrast medium, in pregnant patients and in patients with renal failure (***level of evidence 3**). Its major drawback is prolonged imaging times. In addition to conventional precontrast and post contrast MRI, Diffusion Weighted MRI can also be performed using single shot **S**pin **E**cho (SE) **E**cho **P**lanar **I**maging (EPI) **I**nversion **R**ecovery (IR) sequence, prior to contrast injection with multiple B values (0, 500, 800); the mean Apparent **D**iffusion **C**oefficient (ADC) of renal neoplasm is significant lower than normal renal parenchyma. Cross sectional imaging (CT/MRI) is fairly accurate at renal mass characterization.

In patients on dialysis, iodinated contrast need not be avoided and in these patients, CT scan is preferable to MRI due to small but documented risk of Nephrogenic Systemic Fibrosis (NSF)

eGFR estimation is mandatory prior to the use of intravenous contrast

*Guidelines on Renal Cell Carcinoma. European Association of Urology 2013 March

RCC Staging (American Joint Committee on Cancer **TNM**(**T**umor, **N**ode, **M**etastases) classification)

Stage 1 RCCs are 7 cms or smaller and confined to the kidney.

Stage 2 RCCs are larger than 7 cms but still organ confined.

Stage 3 tumors extend into the renal vein or vena cava, involve the ipsilateral adrenal gland and/or perinephric fat, or have spread to local lymph nodes.

Stage 4 tumors extend beyond the Gerota fascia, have spread to local or distant nodes, or have distant metastases.

(Recent literature has questioned whether the cut-off in size for stage 1 and 2 tumors should be 5 cms instead of 7 cms).

Bosniak classification of renal masses:

Class I includes simple cysts. (Benign)

Class II includes minimally complicated but overwhelmingly benign masses with thin septa, hyperattenuation, or small amounts of mural or septal calcification. (Benign)

Class III includes moderately complicated masses with mural nodularity, thick septa, or irregular or thick

calcifications that often require surgical exploration. (Surgery or close follow up is recommended; a little more than 50% of lesions are malignant)

Class IV includes significantly complicated and generally malignant masses with thick and irregular enhancing regions and definite solid component. (Surgical therapy is recommended, most malignant lesions).

*** European Urology Association guidelines and recommendations on diagnosis, classification, and imaging in patients with renal tumors:**

A change of 20 Hounsfield units (HU) [comparing readings from before contrast administration and after contrast administration (nephrographic phase images)] or greater is strong evidence of enhancement on computed tomography (**level of evidence 3**).

Contrast-enhanced ultrasound can be helpful in specific cases (e.g. chronic renal failure where administration of iodinated contrast and gadolinium is contraindicated (**level of evidence 3**)

In patients with any sign of impaired renal function, an isotope renogram and total renal function evaluation should be considered in order to optimize the treatment decision, e.g. the need to preserve renal function (**level of evidence 2a**).

Renal arteriography and inferior venacavography have only a limited role in the work-up of selected patients with RCC (**level of evidence 3**).

There is a consensus that most bone and brain metastases are symptomatic at diagnosis so that a

routine bone or brain CT scan is not generally indicated. However, if indicated by clinical or laboratory signs and symptoms, other diagnostic procedures may be used, such as a bone scan, brain CT, or MRI (**level of evidence 3**).

Chest CT is most sensitive and is recommended for assessment of the lung, but a plain chest x-ray can be sufficient in low-risk patients**. Recommendation Grade A**.

Abdominal CT or MRI is recommended for the workup of patients with RCC. **Recommendation Grade A.**

Evaluation of renal function is recommended before treatment planning. **Recommendation Grade B**

Percutaneous biopsy is always indicated before ablative and systemic therapy without previous histopathology and in surveillance strategies**. Recommendation Grade B.**

Bosniak classification of renal cysts is advocated for the workup of cystic renal masses**. Recommendation Grade C**

Except for angiomyolipomas, most uncommon renal tumors cannot be differentiated from Renal Cell Carcinoma based on imaging. **Recommendation Grade C**

The current TNM (Tumor, Node, Metastasis) classification system is recommended for staging. **Recommendation Grade B**

The **Fuhrman grading system** (Pathology grading system based on the microscopic morphology of a

neoplasm with hematoxylin and eosin (H&E) staining) and Renal Cell Carcinoma type classification should be used. **Recommendation Grade B**

No molecular prognostic marker, at present, is recommended for routine clinical use. **Recommendation Grade B**

* Reproduced with permission

Suggested Reading:

Guidelines on renal cell carcinoma.
Ljungberg B, Bensalah K, Bex A, Canfield S, Dabestani S, Hofmann F, Hora M, Kuczyk MA, Lam T, Marconi L, Merseburger AS, Mulders PFA, Staehler M, Volpe A. Guidelines on renal cell carcinoma. Arnhem (The Netherlands): European Association of Urology (EAU); 2013 Mar. 56 p. [378 references]

Chaan S. Ng1, Christopher G. Wood, Paul M. Silverman1, Nizar M. Tannir, Pheroze Tamboli and Carl M. Sandler, **Number 4 Genitourinary Imaging Review: Renal Cell Carcinoma: Diagnosis, Staging, and Surveillance**- October 2008, AJR: Volume 191

Sobin LH, Gospodariwicz M, Wittekind C, editors. **TNM classification of malignant tumors.**UICC International Union Against Cancer.7th ed. New York: Wiley-Blackwell; 2009. p. 255–7.

Hilton S**. Imaging of renal cell carcinoma**. Semin Oncol 2000; 27:150–159

Peycelon M, Hupertan V, Comperat E, **et al. Long-term outcomes after nephron sparing surgery for**

renal cell carcinoma larger than 4 cm. J Urol 2009;181:35–41.

Hendrik Van Poppel, Luigi Da Pozzo , Walter Albrecht, Vsevolod Matveev , Aldo Bono , Andrzej Borkowski, Marc Colombel , Laurence Klotz , Eila Skinner , Thomas Keane , Sandrine Marreaud , Sandra Collette and Richard Sylvester: **A Prospective, Randomised EORTC Intergroup Phase 3 Study Comparing the Oncologic Outcome of Elective Nephron-Sparing Surgery and Radical Nephrectomy for Low-Stage Renal Cell Carcinoma**: European Urology: Volume 59, issue 4, pages e15-e26, April 2011.

Carlo Terrone, Alessandro Volpe: Department of Urology, University of Eastern Piedmont, Maggiore della Carita' Hospital, Novara, Italy: **Can Emerging Level 1 Evidence "Discourage" Elective Nephron-Sparing Surgery for Small Renal Tumors?** EUROPEAN UROLOGY volume, 59 (2011) 553 -555.

Imaging renal cell carcinoma with ultrasonography, CT and MRI.

Nat Rev Urol. 2010 Jun;7(6):311-25. doi: 10.1038/nrurol.2010.63. Epub 2010 May 18.

Leveridge MJ, Bostrom PJ, Koulouris G, Finelli A, Lawrentschuk N.

Abstract

The increased use of abdominal imaging techniques for a variety of indications has contributed to more-frequent detection of renal cell carcinoma (RCC).

Ultrasonography has been used to characterize the solid versus cystic nature of renal masses. This modality has limitations, however, in further characterization of solid tumors and in staging of malignancy, although contrast-enhanced ultrasonography has shown promise. Cross-sectional imaging with multiplanar reconstruction capability via CT or MRI has become the standard-bearer in the diagnosis, staging and surveillance of renal cancers. The use of specific protocols and the exploitation of different imaging characteristics of RCC subtypes, including variations in contrast agent timing, MRI weighting and digital subtraction, have contributed to this diagnostic capability. Cystic renal masses are a special case, evaluation of which can require multiple imaging modalities. Rigorous evaluation of these lesions can provide information that is crucial to prediction of the likelihood of malignancy. Such imaging is not without risk, however, as radiation from frequent CT imaging has been implicated in the development of secondary malignancies, and contrast agents for CT and MRI can pose risks, particularly in patients with compromised renal function.

PMID:20479778 [Pub Med - indexed for MEDLINE]

Curr Urol Rep. 2011 Feb;12(1):11-7. doi: 10.1007/s11934-010-0148-y.

Contemporary imaging of the renal mass.

Kang SK, Kim D, Chandarana H.

Abstract

Renal masses increasingly are detected incidentally in asymptomatic individuals. Accurate characterization of these lesions is important for clinical management, planning intervention, and avoiding unnecessary procedures. Ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI) are the mainstays of renal mass detection and characterization. Ultrasonography is useful for distinguishing cystic from solid lesions and can detect lesion vascularity, especially with use of ultrasound contrast agents, but is less sensitive, less specific, and less reproducible than CT and MRI. CT, with and without intravenous contrast, is the primary imaging test for characterization and staging of renal lesions, and is utilized more often than MRI. Current multidetector CT technology provides near isotropic acquisition, with three-dimensional reformatting capabilities. Due to lack of exposure to iodinated contrast and ionizing radiation and superior soft tissue contrast, MRI is being increasingly utilized as a problem-solving tool for diagnosis, staging, and preoperative planning for renal malignancies. Future directions for imaging of primary renal neoplasm include accurate characterization of renal cell cancer subtype, assistance with treatment planning, and evaluation of treatment response.

PMID:20949339[PubMed - indexed for MEDLINE]
Br J Radiol. 2003 Oct; 76(910): 696-703.

Imaging of renal lesions: evaluation of fast MRI and helical CT.

Walter C, Kruessell M, Gindele A, Brochhagen HG, Gossmann A, Landwehr P.

Abstract

The purpose of this study is to compare triphasic helical CT and fast MRI with respect to detection, characterization and staging of suspected renal masses. To achieve this triphasic helical CT (plain, corticonephrographic and tubulonephrographic phase) and MRI with fast T(1) weighted and T(2) weighted sequences were performed in 29 patients with a suspected renal lesion. Image quality, lesion characterization and lesion extent were assessed for both methods in all patients. The acquisition phase for CT and the image sequence for MRI offering the best image quality and best diagnostic information regarding renal parenchyma, renal vessels, detection of enlarged lymph nodes, and other abdominal organs were determined. Histologically confirmed renal cell carcinomas (n=18) were staged based on the Robson classification. Quantitative data were obtained from operator-defined regions of interest (ROIs) in all acquisition phases (CT) and all image sequences (MRI). For most criteria the rating of image quality for helical CT was generally higher as compared with fast MRI. CT and MRI detected all 24 histologically proven masses, while no false positive solid tumor was diagnosed with both imaging modalities. All three acquisition phases in CT and all applied image sequences in MRI were regarded as necessary in order to gain important diagnostic information. Altogether, 12 of 18 renal cell carcinomas (67%) were correctly staged by CT and MRI. Helical CT and fast MRI allow the correct detection and characterization of suspicious renal lesions. Both imaging modalities can be

recommended for clinical routine application. Although the correct histological staging of renal cancer remains difficult for both imaging methods, both are excellent in providing the critical staging information needed before surgery. Helical CT offers a significantly shorter acquisition time to cover the entire abdomen.

PMID:14512329[PubMed - indexed for MEDLINE]

MR imaging of renal masses: correlation with findings at surgery and pathologic analysis. Radiographics: 2008 Jul-Aug; 28(4):985-1003.

Pedrosa I, Sun MR, Spencer M, Genega EM, Olumi AF, Dewolf WC, Rofsky NM.

Abstract

Magnetic resonance (MR) imaging is useful in the characterization of renal masses. The MR imaging manifestations and pathologic diagnoses of 82 renal masses were reviewed and correlated. The MR imaging appearance of clear cell type renal cell carcinoma varies depending on the presence of cystic components, hemorrhage, and necrosis. Papillary renal cell carcinomas appear as well-encapsulated masses with homogeneous low signal intensity on T2-weighted images and homogeneous low-level enhancement after the intravenous administration of contrast material, or as cystic hemorrhagic masses with peripheral enhancing papillary projections. Transitional cell carcinoma may be seen as an irregular, enhancing filling defect in the pelvicaliceal system or ureter. Lymphomatous masses are usually hypointense relative to the renal cortex on T2-weighted images and enhance

minimally on delayed gadolinium-enhanced images. Bulk fat is a distinguishing feature of angiomyolipoma. Oncocytoma has a variable and nonspecific appearance at MR imaging. MR imaging findings may allow the characterization of various renal masses and can provide valuable information for their clinical management.

PMID: 18635625 [Pub Med - indexed for MEDLINE]

Anticancer Res. 2004 Nov-Dec;24(6):4175-9.

Correlation of diffusion-weighted MR imaging with cellularity of renal tumours.

Squillaci E, Manenti G, Cova M, Di Roma M, Miano R, Palmieri G, Simonetti G.

Abstract

Background:

Diffusion is a physical process based on the random movement of water molecules known as Brownian movement. Diffusion-weighted imaging (DWI) is a magnetic resonance (MR) technique that provides information about the biophysical properties of tissues such cell organization and density, microstructure and microcirculation.

Materials and Methods:

Twenty healthy volunteers and 18 patients with renal tumor were enrolled in our study. The DWI was obtained before contrast media injection with a single-shot SE EPI Inversion Recovery (IR) sequence. The tumor cellularity of each resected lesion was evaluated.

Results:

The mean apparent diffusion coefficient (ADC) value of renal tumors was significantly lower than the mean ADC value of normal renal parenchyma. In our series, the mean ADC value of renal tumors did not significantly correlate with tumor cellularity, but correlated with histological architecture.

Conclusion:

These preliminary results indicate the utility of DWI in the acquisition of tissue characterization data of renal masses using a minimal acquisition time (17 sec).

PMID: 15736469 [PubMed - indexed for MEDLINE]

Adv Urol. 2008: Epub 2009 Mar 29.

Radiologic evaluation of small renal masses (I): pretreatment management.

Marhuenda A, Martín MI, Deltoro C, Santos J, Rubio Briones J.

Abstract

When characterizing a small renal mass (SRM), the main question to be answered is whether the mass represents a surgical or nonsurgical lesion or, in some cases, if followup studies are a reasonable option. Is this a task for a urologist or a radiologist? It is obvious that in the increasing clinical scenario where this decision has to be made, both specialists ought to work together. This paper will focus on the principles, indications, and limitations of ultrasound, CT, and MRI to characterize an SRM in 2008 with a detailed review

of relevant literature. Special emphasis has been placed on aspects regarding the bidirectional information between radiologists and urologists needed to achieve the best radiological approach to an SRM.

PMID: 19343187 [PubMed]

Adv Urol. 2008:196701. doi: 10.1155/2008/196701.

Surveillance for the management of small renal masses.

Ozsoy M, Klatte T, Waldert M, Remzi M.

Abstract

Surveillance is a new management option for small renal masses (SRMs) in aged and infirm patients with short-life expectancy. The current literature on surveillance of SRM contains mostly small, retrospective studies with limited data. Imaging alone is inadequate for suggesting the aggressive potential of SRM for both diagnosis and followup. Current data suggest that a computed tomography (CT) or magnetic resonance imaging (MRI) every 3 months in the 1st year, every 6 months in the next 2 years, and every year thereafter, is appropriate for observation. The authors rather believe in active surveillance with mandatory initial and followup renal tumor biopsies than classical observation. Since not all SRMs are harmless, selection criteria for active surveillance need to be improved. In addition, there is need for larger studies in order to better outline oncological outcome and followup protocols.

PMID:18704192 [Pub Med]

AJR Am J Roentgenol. 2008 Oct;191(4):1220-32. doi: 10.2214/AJR.07. 3568.

Renal cell carcinoma: diagnosis, staging, and surveillance.

Ng CS, Wood CG, Silverman PM, Tannir NM, Tamboli P, Sandler CM.

Source

Department of Radiology, Box 368, The University of Texas M D Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030-4009, USA. cng@mdanderson.org

Abstract

Objective:

This educational review focuses on the staging and radiologic evaluation of renal cell carcinoma. It includes discussion of the epidemiology, pathology, and therapeutic options of renal cell carcinoma and the implications for radiologic follow-up.

Conclusion:

The incidence of renal cell carcinoma has been increasing. Imaging plays a central role in its detection, staging, treatment evaluation and follow-up.

Imaging in Bladder Cancer

Introduction

Bladder cancer is the commonest urological malignancy in India and presents as superficial (non-muscle invasive), muscle invasive or metastatic disease. Cigarette smoking is thought to be responsible for 50–66% of all bladder cancers in men and 35% of all bladder cancers in women. Occupational exposures likely account for another 20% of cases, with patients exposed to aromatic amines (petrochemical, textile, printing industries) at greatest risk. Other occupations increasing the risk for bladder cancer include hairdressing, firefighting, truck driving, and plumbing because of chemical exposure in the workplace. Other known risk factors include exposure to certain medications (phenacetin and cyclophosphamide) and arsenic, prior pelvic irradiation, and chronic lower urinary tract inflammation. Alcohol, coffee, and artificial sweeteners are not confirmed risk factors.

Classification

Tumour, Nodes, Metastases classification

The Tumour, Nodes, Metastases (TNM) Classification of bladder cancer is the method most widely used to classify the extent of cancer spread.

2009 TNM classification of urinary bladder cancer:

T - Primary tumour

TX Primary tumor cannot be assessed

T0 No evidence of primary tumor

Ta Non-invasive papillary carcinoma

Tis Carcinoma in situ: 'flat tumor'

T1 Tumor invades subepithelial connective tissue

T2 Tumor invades muscle

T2a Tumor invades superficial muscle (inner half)

T2b Tumor invades deep muscle (outer half)

T3 Tumor invades perivesical tissue

T3a Microscopically

T3b Macroscopically (extravesical mass)

T4 Tumor invades any of the following: prostate, uterus, vagina, pelvic wall, abdominal wall

T4a Tumor invades prostate, uterus or vagina

T4b Tumor invades pelvic wall or abdominal wall

N - Lymph nodes

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

N1 Metastasis in a single lymph node in the true pelvis (hypogastric, obturator, external iliac or presacral)

N2 Metastasis in multiple lymph nodes in the true pelvis (hypogastric, obturator, external iliac or presacral)

N3 Metastasis in a common iliac lymph node (s)

M - Distant metastasis

M0 No distant metastasis

M1 Distant metastasis

Accurate staging of bladder cancer is important as optimal treatment and determination of prognosis depends on it. It is also necessary to differentiate between muscle invasive and non-muscle invasive bladder cancer. The clinical staging of bladder is determined by the depth of invasion of the bladder wall by the tumor using Cystoscopy and biopsy. The non-muscle invasive bladder cancers invade the lamina propria, but do not invade the muscle layer (muscularis propria).

Imaging is used in staging of bladder cancer to evaluate the local extent of disease and to evaluate nodal disease and metastatic spread. The imaging modalities that are used in the evaluation of bladder cancers are Ultrasonography, Computed Tomography and Magnetic Resonance Imaging.

Ultrasonography

For a great majority of patients, presenting with hematuria, if bladder cancer is suspected, ultrasonography is the initial modality that is used for evaluation. The size and location of the lesion determines its efficacy, and the evaluation should be done when the bladder is full. It is very useful for evaluating lesions in bladder diverticulae, which at times are difficult to evaluate cystoscopically. If a mass is detected in the bladder on Ultrasonography, Doppler study should be done to establish flow in the suspected mass to rule out clot or sludge. Transabdominal ultrasonography allows characterization of large renal masses and detection of hydronephrosis and visualization of intravesical filling defects in the bladder(***level of evidence:3**).The limitations of Ultrasonography are that Transabdominal ultrasonography cannot assess the extent of bladder wall invasion and extra-vesical spread accurately, and it cannot assess the entire urinary tract.

*European Association of Urology Guidelines on Bladder cancer 2011

Computed Tomography/ Computed Tomography Urography (CT Urography)

Multi Detector Computed Tomography (MDCT) can evaluate the entire urinary tract and is widely used, but the implications of higher radiation dose needs to considered, when using multiphase technique. CT scan examination should include an unenhanced scan prior

to injection of intravenous contrast. After injection of intravenous contrast at the rate of 3.0 cc per second (total 80-100 cc of contrast), images are acquired at 30 seconds after the start of contrast injection (cortico-medullary/ arterial phase), followed by a nephrographic phase acquisition at 80 to 120 seconds after the start of contrast injection and then an excretory phase acquisition at 5 to 10 minutes after intravenous contrast injection.The images obtained should be thin sections (2.5 or 3.0 mm) with retro-reconstruction of 0.625 or 0.75 mm. The bladder cancer enhances in the arterial phase, earlier than the bladder wall with the maximum enhancement at 80 to 90 seconds. The patient should not void urine approximately 45 to 60 minutes prior to CT scan, as the un-opacified urine in the bladder acts as a negative contrast. CT Urography should be performed with thin section images in the excretory phase, these excretory phase thin section images should be obtained if possible with homogenous opacification of the bladder with excreted contrast material.

The advantages of CT scan are that, in addition to the evaluation of the entire urinary tract, it can detect metastasis, and if the adjacent organs are involved. It is more sensitive than Ultrasonography and Intravenous Urography; however it is not very accurate for local staging. CT scan should ideally be performed prior to Trans Urethral Resection of Bladder Tumor (TURBT) as the information obtained from CT scan such as hepatic and nodal metastases can alter patient management.

CT scan cannot accurately assess the depth of bladder invasion (differentiating T2a from T2b, however, differentiation between T3a and T3b is possible as T3b tumors are seen on CT images as irregularity of the outer wall of the bladder, perivesical fat stranding and soft tissue mass). The reason for ideally imaging prior to TURBT is that the TURBT can cause bladder wall enhancement at the resection site and perivesical fat stranding, these post TURBT findings make CT scan less specific.

The overall accuracy of CT scan in local staging is 60%. Distending the bladder and not performing a CT scan immediately after TURBT can improve accuracy. The accuracy of CT urography is higher than intravenous urography (***level of evidence: 2b**). MDCT yields isotropic voxels and post processing of MDCT volumetric data allow three dimensional (3D) reconstructions, however, basing one's assessment only on 3D reconstructions alone is inferior as compared to assessment using 3D reconstructions together with thin section axial images. The accuracy of CT scan for lymph node assessment varies from 73 to 92% (criteria: short axis measurement of 1.0 cm).

CT scan is also performed as an additional investigation when ultrasonography detects bladder tumor for evaluation of upper urinary tract. In a setting of hematuria with negative ultrasound, IVU may be considered as an investigation due to radiation dose concern with CT scan/CT urography. CT is also used to evaluate the common sites of distant spread of disease.

*European Association of Urology Guidelines on Bladder cancer 2011

Magnetic Resonance Imaging (MRI)

MR imaging has superior soft tissue contrast, its direct multiplanar imaging capability and the possibility of routine high resolution acquisition allows for better evaluation of trigone region and dome of the bladder. The adjacent structures such as prostate, seminal vesicles are also better evaluated. The imaging protocol for bladder evaluation should include T1-weighted and T2-weighted images in multiple planes and single shot fluid attenuation inversion recovery sequence that attenuates signal of the urine in the bladder, as it can better delineate and characterize bladder tumor. Dynamic Contrast enhanced (DCE)-MRI and Diffusion Weighted (DW)-MRI are newer techniques that allow better evaluation of disease, hence these techniques should also be included in the routine imaging protocol.

The appearance of bladder tumor on MR imaging, the tumor shows intermediate signal intensity on T1W images, similar to muscle but these images can delineate intravesical component and perivesical fat stranding. The bladder tumors show higher signal intensity as compared to normal muscularis and show intermediate to high signal intensity on T2W images, and the bladder wall appears low in signal intensity on T2W images and when the signal intensity of bladder wall is maintained adjacent to tumor, muscle infiltration can be ruled out. Infiltration of adjacent

organs can also be depicted on T2W images. On Dynamic Contrast Enhanced MR imaging, bladder tumors show early enhancement as compared to normal bladder wall; hence this early enhancement can differentiate bladder tumor from adjacent soft tissues. On DW-MRI; bladder tumors show restricted diffusion.

The overall accuracy of MR Imaging for local staging of bladder tumors, reported in literature varies between 73 to 96% and for overall staging, the accuracy varies between 60 to 85% and for staging, extravesical extension, the accuracy is 73 to 100%. If imaging is performed early in post biopsy setting, there is over staging. MR imaging can also delineate lymph node metastases in enlarged nodes, but micrometastasis in normal sized nodes is missed. The accuracy of MR imaging of for nodal staging is between 73 to 90% (pelvic nodes greater than 8 mm and abdominal nodes 10 mm in maximum short axis diameter should be regarded as enlarged. MR imaging can also delineate hepatic metastases (DCE-MRI) and osseous metastases (T1W images).

eGFR estimation is mandatory prior to the use of intravenous contrast

Conclusion:

Ultrasonography,in spite of its short comings, remains the initial investigation for a large majority.CT scan/ CT Urography is one examination that can evaluate causes of hematuria such as lithiasis, benign conditions, kidney lesions and urothelial neoplasms; however CT

scan can miss lesions in the bladder and hence it cannot obviate the use of cystoscopy in the evaluation of suspected bladder tumors. MDCT is superior to MR imaging in the evaluation of upper urinary tract due to its superior spatial resolution. MR imaging is superior is to CT scan for local staging of bladder cancer, but the newer advanced MR imaging techniques (DCE-MRI and DW-MRI) are still evolving.

*** European Urology Association: Guidelines and Recommendations**

Imaging guideline for Non-Muscle Invasive Bladder Cancer:

Guidelines for primary assessment of non-muscle-invasive bladder cancers

At the time of initial diagnosis of bladder cancer, CT urography or IVU should be performed only in selected cases (e.g., tumors located in the trigone).**Grade B recommendation.**

Guidelines for follow-up patients with non-muscle invasive bladder cancer

Regular (yearly) upper tract imaging (CT-IVU or IVU) is recommended for high-risk tumors. **Grade C recommendation.**

During follow-up in patients with positive cytology and no visible tumor in the bladder, R-biopsies or biopsies with PDD photodynamic diagnosis (if equipment is available) and investigation of extravesical locations (CT urography, prostatic urethra biopsy) are recommended. **Recommendation Grade B**

Imaging guideline Muscle Invasive Bladder Cancer:

For Diagnosis of invasive bladder cancer

Imaging to be performed only if staging will make a difference to the selection of treatment option.

For staging of verified bladder tumor

For optimal local staging (in patients considered eligible for radical treatment), either MR imaging with fast dynamic contrast-enhancement or MDCT with contrast enhancement are recommended for patients considered suitable for radical treatment.

Recommendation GRADE B

For patients with confirmed muscle-invasive bladder cancer, MDCT of the chest, abdomen and pelvis is the optimal form of staging, including MDCT urography for complete examination of the upper urinary tracts. If MDCT is not available, lesser alternatives are excretory urography and a chest X-ray

Recommendation GRADE B

In patients with a verified muscle invasive lesion(TUR), abdominal pelvis and chest imaging is mandatory. MR imaging and CT are equivalent in diagnosing local and distant abdominal metastases **Recommendation GRADE C**

Computed tomography is preferred to magnetic resonance imaging for the detection of pulmonary metastases. **Recommendation GRADE C**

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Verma S, Rajesh A, Prasad SR, Gaitonde K, Lall CG, Mouraviev V, Aeron G, Bracken RB, Sandrasegaran K : **Urinary bladder cancer: role of MR imaging** - Radiographics. 2012 Mar-Apr; 32(2):371-87.

Shaista Hafeez and Robert Huddart* Corresponding author: Robert Huddart the Royal Marsden NHS Foundation Trust and the Institute of Cancer Research, Sutton, Surrey, UK.-**Advances in bladder cancer imaging.**

Verma S, Rajesh A, Prasad SR, Gaitonde K, Lall CG, Mouraviev V, Aeron G, Bracken RB, Sandrasegaran K. **: Urinary bladder cancer: role of MR imaging** - Radiographics. 2012 Mar-Apr; 32(2) : 371-87.

Abstract

Urinary bladder cancer is a heterogeneous disease with a variety of pathologic features, cytogenetic characteristics, and natural histories. It is the fourth most common cancer in males and the tenth most common cancer in females. Urinary bladder cancer has a high recurrence rate, necessitating long-term surveillance after initial therapy. Early detection is important, since up to 47% of bladder cancer-related deaths may have been avoided. Conventional computed tomography (CT) and magnetic resonance (MR) imaging are only moderately accurate in the diagnosis and local staging of bladder cancer, with cystoscopy and pathologic staging remaining the standards of reference. However, the role of newer MR imaging sequences (e.g., diffusion-weighted imaging) in the diagnosis and local staging of bladder cancer is still evolving. Substantial advances in MR imaging technology have made multiparametric MR imaging a feasible and reasonably accurate technique for the local staging of bladder cancer to optimize

treatment. In addition, whole-body CT is the primary imaging technique for the detection of metastases in bladder cancer patients, especially those with disease that invades muscle.

PMID: 22411938 [PubMed - indexed for MEDLINE]

Shaista Hafeez and Robert Huddart: Advances in bladder cancer imaging - **the Royal Marsden NHS Foundation Trust and the Institute of Cancer Research, Sutton, Surrey, UK.**

Abstract

The purpose of this article is to review the imaging techniques that have changed and are anticipated to change bladder cancer evaluation. The use of multidetector 64-slice computed tomography (CT) and magnetic resonance imaging (MRI) remain standard staging modalities. The development of functional imaging such as dynamic contrast-enhanced MRI, diffusion-weighted MRI and positron emission tomography (PET)-CT allows characterization of tumor physiology and potential genotypic activity, to help stratify and inform future patient management. They open up the possibility of tumor mapping and individualized treatment solutions, permitting early identification of response and allowing timely change in treatment. Further validation of these methods is required however, and at present they are used in conjunction with, rather than as an alternative to, conventional imaging techniques.

AcadRadiol: 2012 Sep; 19(9):1134-40. Epub 2012 Jun 19.

Comparative effectiveness of imaging modalities for the diagnosis of upper and lower urinary tract malignancy: a critically appraised topic.

Razavi SA, Sadigh G, Kelly AM, Cronin P

Abstract

Rationale and Objectives:

The purpose of this study was to critically appraise and compare the diagnostic performance of imaging modalities that are used for the diagnosis of upper and lower/bladder urinary tract cancer, transitional cell carcinoma (TCC).

Methods:

A focused clinical question was constructed and the literature was searched using the patient, intervention, comparison, outcome (PICO) method comparing computed tomography (CT) urography, magnetic resonance (MR) urography, excretory urography, and retrograde urography in the detection of TCC of the upper urinary tract. The same methods were used to compare CT cystography, MR cystography, and ultrasonography in the diagnosis of bladder cancer. Retrieved articles were appraised and assigned a level of evidence based on the Oxford University Centre for Evidence-Based Medicine hierarchy of validity for diagnostic studies.

Results:

The retrieved sensitivity/specificity for the detection of TCC of upper urinary tract for CT urography, MR urography, excretory urography, and retrograde urography were 96%/99%, 69%/97%, 80%/81%, and 96%/96%, respectively. For detecting bladder cancer, the retrieved sensitivity/specificity for CT cystography, MR Cystography, and ultrasonography were 94%/98%, 91%/95%, and 78%/96%, respectively.

Conclusions:

CT urography is the best imaging technique for confirming or excluding malignancy in the upper urinary tract, whereas CT cystography has the best diagnostic performance for diagnosing bladder cancer.

PMID: 22717592 [Pub Med - indexed for MEDLINE]

International Journal of Urology (2010) 17, 102–124. **Volume 17, Issue 2**.

Guidelines: Evidence-based clinical practice guidelines for bladder cancer (Summary – JUA 2009 Edition) The Committee for Establishment of the Clinical Practice Guidelines for the Management of Bladder Cancer and the **Japanese Urological Association (JUA)**.

Transabdominal ultrasonography is a simple and effectiveimaging modality, but in some bladder cancers its accuracy might suffer depending on the tumor size and site. Intravenous urography (IVU) is useful in eliminating further urothelial tumors arising in the upper urinary tract, but is not necessary in all patients

because the incidence of upper urinary tract tumors at the time of diagnosis of a bladder cancer is of the order of 0.3–2.3%. The diagnostic accuracy of staging of the primary tumorusing CT and MRI is not particularly high. However, both modalities are useful in detecting bladder cancer extramural invasion and lymph node metastases, and should be performed whenever muscle invasive bladder cancer is suspected, before transurethral resection of bladder tumor.

When muscle-invasive bladder cancer is suspected clinically, T staging is performed using pelvic computed tomography (CT) or magnetic resonance imaging (MRI) scanning. As bladder cancer tends to metastasize to lymph nodes, the liver and lung, CT scanning of the chest and abdomen is useful for N and M staging **(Grade of recommendation B)**

The Role of Multiparametric MR Imaging in the Diagnosis of the Prostate Carcinoma

Introduction:

Prostate cancer is the most common malignancy among men in the USA, with an estimated 217,730 new cases and 32,050 prostate cancer related deaths in 2010. The incidence of Ca Prostate increases with age, and it is very uncommon in men younger than 50 years old. Most men diagnosed with Ca prostate ultimately survive the disease and die of other causes. The overall 5-year survival rate is 99% for all stages, but only 34% when there are distant metastases. About 15% of male cancers are prostate cancers in developed countries compared to 4% of male cancers in developing countries.

In India, prostate cancer is identified as only the 10th common malignancy affecting men. There is no comprehensive information available on the actual incidence of prostate cancer in India. Efforts have been made by the Indian Council of Medical Research (ICMR)

to collect data through the National Cancer Registry. At the Tata Memorial Hospital, prostate cancer constitutes only 2.4% of all cancers in males. The aim of Ca prostate management is to identify, treat, and cure patients with aggressive disease that may prove fatal but to avoid overtreating those in whom the disease is unlikely to be life threatening. Most patients diagnosed with Ca prostate have localized disease confined to the prostate. A small number with high-grade tumors will progress to develop local, extracapsular tumor extension and distant metastases. Prostate tumors are graded according to their pathological appearance with a Gleason score (GS), which represents the sum of the dominant and subdominant histological patterns (grades). High GSs indicate aggressive tumors with increased potential for local and distant spread; Gleason grading has been shown to provide a spectrum of risk for all patients.

Anatomy of the Prostate:

Approximately 70% of the prostate is formed by glandular tissue, and 30% is composed by nonglandular tissue. According to widely accepted McNeal system, glandular tissue is subdivided into the central and the peripheral gland. The central gland consists of a transitional zone and periurethral tissue, and the peripheral gland is formed by peripheral and central zones. The peripheral zone includes the posterior and lateral aspects of the prostate and accounts for most of the glandular tissue (70%). About 70% of prostate cancers arise in this region. The transitional zone

comprises 5% to 10% of the glandular tissue of the prostate. Cellular proliferation in the transitional zone results in benign prostatic hyperplasia. About 20% of prostate cancers arise in the transitional zone.

Magnetic resonance imaging (MRI):

MR Imaging for the prostate is performed with pelvic phased array coils. The use of endorectal coils improves image resolution on standard 1.5T scanners; however endorectal coils do not provide any added advantage on higher field-strength (3T) scanners. The role of Magnetic resonance imaging (MRI) in prostate cancer is for assessing the extent of disease than for diagnosing the primary disease. For example, organ-confined disease on MRI may imply that the patient can be benefited from surgery (Prostatectomy). MRI proves to be accurate than either digital rectal examination (DRE) or transrectal ultrasound (TRUS) and TRUS guided biopsy, in preoperative anatomical localization of Ca prostate.

As T1-weighted images show no zonal differentiation but they depict high signal intensity blood products, T2-weighted imaging sequence proves to be more important in the imaging protocol for Prostate carcinoma. On T2-weighted images, prostate cancer in the peripheral zone is seen as an area of low signal intensity because of increased cell density and a loss of prostatic ducts, which is easily differentiated from high signal- intensity normal tissue. However T2-weighted imaging sequence has significant limitations for depicting cancer in the transitional and central

zones. This is because cancer and normal tissues both have low signal intensity on T2-weighted images. Moreover, low signal intensity can also be seen in the peripheral zone on T2-weighted images in presence of many noncancerous abnormal conditions, such as nonspecific inflammation, biopsy related hemorrhage, post–radiation therapy fibrosis, and changes after hormone deprivation therapy. The prostate has abundant citrate in normal tissue in the peripheral zone, because of its anticoagulant effect, blood products may persist 4–6 weeks or longer after prostate biopsy, which leads to low signal intensity on T2-weighted images. Areas of high signal intensity on T1-weighted images may represent presence of blood products; however, it is difficult to determine whether the findings represent cancerous tissue or only hemorrhage.

The sensitivity and specificity of T2-weighted MR imaging for prostate cancer detection varies widely. With use of an endorectal coil, the sensitivity of 77%–91% and specificity of 27%–61% was reported for prostate cancer detection with T2-weighted imaging. Most of the reported data about prostate cancer detection reveals occurrence of the prostate cancer in the peripheral zone. According to the results of a study of T2-weighted imaging performed without the use of an endorectal coil, sensitivity and specificity for cancer detection were 45% and 73%, respectively.

In a meta-analysis by Sonnad et al. T2-weighted imaging showed a maximum joint sensitivity and specificity rate of 74% for the staging of Ca Prostate.

To improve the utility of standard MR imaging protocol, newer techniques like Diffusion weighted imaging, Dynamic contrast enhanced imaging and Magnetic resonance spectroscopy are used:

Diffusion-weighted imaging:

Diffusion-weighted imaging (DWI) is an MR-based technique that explores the functional characteristics of tissues. The diffusion properties of tissues can be identified by calculating the apparent diffusion coefficient (ADC). Dickinson et al. showed the standardizing multiparametric magnetic resonance imaging (mpMRI) for Ca Prostate detection, localization, and characterization. Over past few decades, the use of DWI as a tool for the evaluation and management of prostatic cancer has grown steadily. R. Nagrajan et al., recorded the DWI and to compare ADC values derived from DWI in Ca Prostate patients with three different Gleason scores (3 + 3, 3 + 4, and 4 + 3) and concluded that DWI correlates with pathological Gleason scores. Woodfield et al, also worked on the same lines and found the similar results. DWI-acquired ADC values are a very potential measure to delineate prostate carcinoma from the PZ. These can also predict the presence of low and high-grade components in Ca prostate with great accuracy. The ADC values derived from diffusion-weighted MRI can predict tumor aggressiveness and could be useful in treatment decisions and in patient follow-up in active surveillance.

DWI is an in vivo functional imaging technique that can assess molecular diffusion and provides

information about biophysical properties of tissues such as cell organization, density, and microstructure. DWI can be helpful in differentiating high-risk patients from those at low and intermediate risks, since there is a significant correlation between the ADC values from patients with three different Gleason scores. ADC values show a decreasing trend with increasing Gleason scores. These findings suggest that measurement of ADC may provide an additional feature that could further increase the specificity of diagnosis for Ca prostate.

The Mean ADC values and Standard deviation for Gleason's scores found by R. Nagrajan et al was as follows which was statistically significant with P value <0.005.

Gleason scores	ADC values mean ± SD (mm2/sec)
3 + 3	1.135 ±0.119
3 + 4	0.976 ± 0.103
4 + 3	0.831 ± 0.087

Dynamic contrast enhanced MR imaging:

The basis of this technique is based on tumor angiogenesis. In cancer, genetic mutation leads to the production and release of angiogenic factors such as the vascular permeability factor or vascular endothelial growth factor. These factors cause increase in the number of vessels in cancerous tissue. Moreover, the tumor vessels have greater permeability than the normal vessels, because of weak integrity of the vessel wall. Because, the amount of interstitial space is greater

in cancerous tissue than in normal tissue, there is a larger gap of contrast material concentration between the plasma and the interstitial tissue. This characteristic environment makes the enhancement pattern of cancerous tissue different from that of normal tissue. In many experimental studies, it has been shown that the values of contrast enhancement parameters such as mean transit time, blood flow, permeability surface area, and interstitial volume are significantly greater in cancerous tissue than in normal tissue.

This general observation is also applicable to prostate cancer.

With use of fast imaging technique like a gradient-echo sequence, the entire volume of the prostate is imaged in few seconds. The generally accepted requirements for dynamic MRI study are fast imaging sequence, minimal artifacts, and high contrast resolution. At our institution, dynamic MR imaging is performed by applying a three-dimensional fast field echo sequence (3.7/1.9: flip angle, 20°; section thickness, 3.6 mm; no intersection gap; field of view, 30 mm; matrix size 256 X 160)in the axial plane. From this imaging data, various perfusion parameters are acquired according to the time sequence and analyzed to allow the detection and localization of prostate cancer. Various parameters such as baseline signal intensity, peak signal intensity, initial slope, maximum slope within the initial 50 seconds after the contrast injection (slope50), wash-in rate, washout rate, time to peak, percentage of relative enhancement, contrast

agent transfer rate between blood and tissue (Ktrans) and the extravascular extracellular fractional volume (Ve), efflux rate constant from the extravascular extracellular space to the blood plasma (kep), are used for prostate cancer detection and localization. The information is mostly acquired in form of curves; however it can also be obtained in absolute values. Both the methods use the normal prostatic parenchyma as control.

The prostate cancer will show rapid wash-in and rapid washout rates with increased absolute and relative peak enhancement, as compared to the normal prostatic parenchyma. The Ktrans and kep, are elevated in prostate cancer.

Some parameters, such as washout rate and tumor permeability, can also be used to determine the effectiveness of hormone deprivation therapy given for prostate cancer. The results of one study showed marked reduction of tumor permeability and changes of washout pattern after androgen deprivation treatment.

The Dynamic contrast-enhanced MR imaging has the advantage of providing direct depiction of tumor vascularity and may obviate the use of an endorectal coil. However, there are few limitations for this technique such as unsatisfactory depiction of transitional zone cancer in patients with hypervascular benign prostatic hyperplasia. Moreover, there is as yet no consensus with regard to the best acquisition

protocol and the optimal perfusion parameter for differentiating cancer from normal tissue.

eGFR estimation is mandatory prior to the use of intravenous contrast

MR spectroscopy imaging:

MR spectroscopy is non-invasive method of detecting molecular markers; it provides metabolic information about prostatic tissue by displaying the relative concentrations of chemical compounds within contiguous small volumes of interest (voxels). Currently, three-dimensional proton MR spectroscopic metabolic mapping of the entire gland is possible with a resolution of 0.24 mL.MRSI spectra of the prostate gland, the resonances for Choline, Creatine, polyamines and citrate occur at distinct frequencies or positions in the spectrum,at approximately 3.2, 3.0, 3.1 and 2.6 ppm, respectively. Routine Proton MR Spectroscopy mainly shows concentrations of citrate, creatine and Choline. Normal prostate tissue contains high levels of citrate which is higher in the peripheral zone than in the central and transition zones. However glandular hyperplastic nodules, can demonstrate citrate levels as high as those observed in the peripheral zone. In the presence of prostate cancer, the citrate level is diminished or undetectable because of a conversion from citrate- producing to citrate-oxidating metabolism. The Choline level is elevated due to a high phospho-lipid cell membrane turnover in the proliferating malignant tissue. Therefore, the method for depicting

tumors is based on an increased Choline-citrate ratio. Because the creatine peak is very close to the Choline peak in the spectral trace, the two may be inseparable; and for all practical purposes, the ratio of Choline and creatine to citrate is used for spectral analysis in the clinical setting. There is no consensus about spectral interpretation, however the most commonly used classification system is described by Kurhanewicz et al. In this system, a voxel can be classified as normal, suspicious for cancer, or very suspicious for cancer. A voxel may contain nondiagnostic levels of metabolites or artifacts that obscure the metabolite frequency range. Voxels are considered suspicious for cancer if the ratio of Choline and creatine to citrate is at least 2 standard deviations (SDs) higher than the average ratio for the normal peripheral zone. Voxels are considered very suspicious for cancer if the ratio of Choline and creatine to citrate is higher than 3 SDs above the average ratio. Voxels are considered nondiagnostic which contain no metabolites with signal-to-noise ratios greater than 5. In voxels in which only one metabolite is detectable, the other metabolites are assigned a value equivalent to the SD of noise.

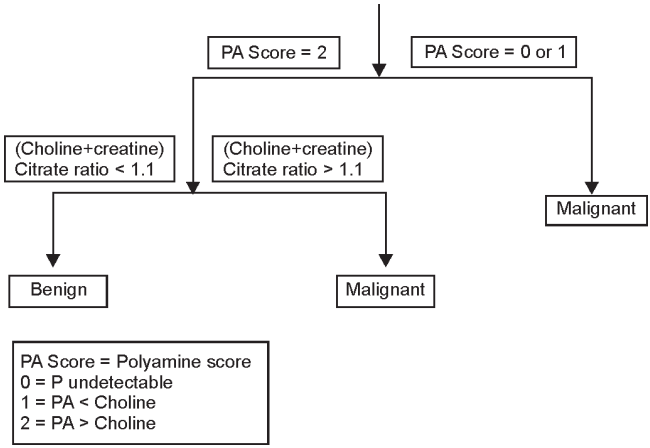
MR spectroscopy enables analysis of the metabolism in the entire prostate gland. Combined with MR imaging, proton MR spectroscopy has shown excellent sensitivity and specificity in the detection of cancer in the peripheral zone of the prostate.

(Choline +Creatine) / Citrate ratio in voxels	Spectroscopic interpretation
2SD higher than normal	suspicious
3SD higher than normal	very suspicious

Few centres are now using newer acquisition and processing software which has also enabled the routine assessment of polyamines (PAs) (predominantly spermine).Several studies have been done to investigate the role of PAs in cellular growth and differentiation in prostate cancer which have revealed that in normal and benign hyperplastic tissue, a high content of spermine is present, whereas spermine levels in malignant tumor are reduced.

If the PA peak is lower than the Choline peak or is undetectable, the voxel is said to be malignant. If the PA peak is higher than the Choline peak, the voxel is considered benign if the (Cho+Cr)/Citrate is less than 1.1 and malignant if the (Cho+ Cr)/Citrate is greater than or equal to 1.1.

In the decision tree for classifying voxels as benign or malignant , the first branching of the tree is based on the PA score, indicating that this factor was determined to have greater importance than the (Choline+ Creatine)/Citrate.



***Guidelines and recommendations on prostate cancer: european association of urology**

Guidelines for the diagnosis of prostate cancer:

An abnormal digital rectal examination (DRE) result or elevated serum PSA measurement could indicate Prostate Carcinoma. The exact cut-off level of what is considered to be a normal PSA value has yet to be determined, but values of approximately < 2-3 ng/mL are often used for younger men. The diagnosis of Prostate Carcinoma depends on histopathological (or cytological) confirmation.

Diagnosis of prostate cancer - recommendations

Biopsy and further staging investigations are only indicated if they affect the management of the patient. Recommendation Grade C

Transrectal ultrasound (TRUS)-guided systemic biopsy is the recommended method in most cases of suspected Prostate Cancer. A minimum of 8 systemic, laterally directed, cores are recommended, with perhaps more cores in larger volume prostates. Recommendation Grade B

Transition zone biopsies are not recommended in the first set of biopsies due to low detection rates. Recommendation Grade C.

One set of repeat biopsies is warranted in cases with persistent indication for Prostate Cancer (abnormal DRE, elevated PSA or histopathological findings suggestive of malignancy at the initial biopsy). Recommendation Grade B.

Overall recommendations for further (three or more) sets of biopsies cannot be made; the decision must be made based on an individual patient. Recommendation Grade C.

Transrectal peri-prostatic injection with a local anaesthetic can be offered to patients as effective analgesia when undergoing prostate biopsies. Recommendation Grade A

Guidelines for the staging of prostate cancer:

Despite its high specificity in the evaluation of extra prostatic extension (EPE) and seminal vesicle invasion (SVI), TRUS (Trans Rectal Ultrasonography) has low sensitivity and a tendency to under stage prostate cancer. Even with the advent of color power Doppler and contrast enhancement the accuracy of TRUS in

local staging remains inadequate and largely operator-depended.

In comparison with DRE, TRUS and computed tomography (CT), MRI demonstrates higher accuracy for the assessment of uni- or bi-lobar disease (T2), EPE and SVI (T3), as well as the invasion of adjacent structures (T4).

Currently only sentinel lymph node dissection or extended PLND allow for histological detection of lymph node metastases with high sensitivity.

Staging of Prostate Cancer– Recommendations

Local staging (T-staging) of Prostate Cancer should be based on magnetic resonance (MR) imaging. Further information is provided by the number and sites of positive prostate biopsies, the tumor grade and the level of serum PSA. Recommendation Grade C.

For local staging TRUS should not be used since it has low sensitivity and a tendency to under stage Prostate Cancer.

Lymph node status (N-staging) need only be assessed when potentially curative treatment is planned.

Patients with stage T2 or less, PSA < 20 ng/mL and a Gleason score < 6 have a lower than 10% likelihood of having node metastases and can be spared nodal evaluation. Recommendation Grade B.

In clinically localized Prostate Cancer, staging must be done by pelvic lymph node dissection since it presents the only reliable staging method, given the significant

limitations of pre-operative imaging in the detection of small metastases (< 5 mm),

Skeletal metastasis (M-staging) is best assessed by bone scan. This may not be indicated in asymptomatic patients if the serum PSA level is < 20 ng/mL in the presence of well or moderately differentiated tumors. Recommendation Grade B.

In equivocal cases, 11C-choline-, 18F-flouride-PET/CT or whole bodies MRI are an option. Recommendation Grade C.

[CT = computed tomography; DCE-MRI = dynamic contrast-enhanced MRI; DRE = digital rectal examination;

EPE = extra prostatic extension; MRI = magnetic resonance imaging; MRSI = magnetic resonance spectroscopic

Imaging; PET = positron emission tomography; PLND = pelvic lymph-node dissection; PSA = prostate-specific antigen; SVI = seminal vesicle invasion; TRUS = Transrectal ultrasound.]

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Accuracy of MR imaging for staging prostate cancer: a meta-analysis to examine the effect of technologic change.

Sonnad SS, Langlotz CP, Schwartz JS. Source: Consortium for Health Outcomes, Innovation and Cost-Effectiveness Studies, Department of Surgery, University of Michigan, Ann Arbor 48109-0346, USA.

Abstract

Rationale and Objectives:
The purpose of this study was to summarize the accuracy of magnetic resonance (MR) imaging for staging prostate cancer and to determine the effect of high magnetic field strength, use of the endorectal coil, use of fast spin-echo (SE) imaging, and study size on staging accuracy.

Materials and Methods:
A literature search and review yielded 27 studies comparing MR imaging to a pathologic standard in

patients with clinically limited prostate cancer. Subgroup analyses examined magnetic field strength, use of an endorectal coil, use of fast SE imaging, publication date, and study size.

Results:

A summary receiver operating characteristic curve for all studies had a maximum joint sensitivity and specificity of 74%. At a specificity of 80% on this curve, sensitivity was 69%. Subgroup analyses showed that fast SE imaging was statistically significantly more accurate than conventional SE techniques ($P < .001$). Unexpectedly, studies employing higher magnetic field strength and those employing an endorectal coil were less accurate.

Conclusion:

Seemingly small technologic advances may influence test accuracy. Early and small studies, however, may overstate accuracy because of publication bias, bias in small samples, or earlier studies being performed by the experts who developed the technology itself.

Local staging of prostate cancer using magnetic resonance imaging: a meta-analysis.

Engelbrecht MR, Jager GJ, Laheij RJ, Verbeek AL, van Lier HJ, Barentsz JO.

EurRadiol. 2002 Sep;12(9):2294-302. Epub 2002 Apr 19.Source

Department of Radiology, University Hospital Nijmegen, P.O. Box 9101, 6500 HB, Nijmegen, The Netherlands. M.Engelbrecht@rdiag.azn.nl

Abstract

Our objective was to determine the influence of patient, study design-, and imaging protocol characteristics on staging performance of MR imaging in prostate cancer. In an electronic literature search and review of bibliographies (January 1984 to May 2000) the articles selected included data on sensitivity and specificity for local staging.

Subgroup analyses examined the influence of age, prostate specific antigen, tumor grade, hormonal pre-treatment, stage distribution, publication year, department of origin, verification bias, time between biopsy and MR imaging; consensus reading, study design, consecutive patients, sample size, histology preparation, imaging planes, fast spin echo, fat suppression, endorectal coil, field strength, resolution, glucagon, contrast agents, MR spectroscopy, and dynamic contrast-enhanced MRI.

Seventy-one articles and five abstracts were included, yielding 146 studies. Missing values were highly prevalent for patient characteristics and study design. Publication year, sample size, histologic gold standard, number of imaging planes, turbo spin echo, endorectal coil, and contrast agents influenced staging performance (p=0.05).

Due to poor reporting it was not possible to fully explain the heterogeneity of performance presented in the literature. Our results suggest that turbo spin echo, endorectal coil, and multiple imaging planes improve staging performance. Studies with small sample sizes may result in higher staging performance.

Diagnostic accuracy of surface coil magnetic resonance imaging at 1.5 T for local staging of elevated risk prostate cancer

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Abstract

Introduction:

Preoperative prostate cancer stage predicts prognosis and affects treatment decisions. The purpose of this study was to estimate the sensitivity and specificity of surface coil magnetic resonance imaging (MRI) for prostate cancer stage using surgical pathologic data as the reference standard.

Methods:

High-risk patients (≥ cT3 or PSA ≥ 20 ng/mL or Gleason ≥ 8) and selected intermediate-risk patients (clinically bulky disease on exam or biopsy, cT2b/c, or Gleason 7 with ≥ 3 of 5 biopsy cores positive in a lobe) routinely received a pelvic MRI at our institution. The images of identified patients were reviewed by one radiologist who was blinded to clinical information. The radiologist reported presence or absence of tumour within each lobe of the prostate. Extra Prostatic Extension (EPE), seminal vesicle (SV) invasion and pelvic lymph node (PLN) metastasis were also reported. Radiological findings were compared with prostatectomy pathology reports.

Results:

During the study period, about 320 radical prostatectomies were performed. Of these, 32 had a preoperative surface coil pelvic MRI adequate for analysis. Pathologically, 53 of 64 (82.8%) prostate lobes contained tumour, 17 (26.6%) lobes had associated EPE, 12 (18.8%) had SV involvement and 7 (10.9%)

sets of PLNs contained cancer. Magnetic resonance imaging sensitivity and specificity were, respectively, 94.3% and 81.8% for tumour location, 82.4% and 87.2% for EPE, 83.3% and 92.3% for SV invasion and 71.4% and 94.7% for PLN involvement.

Interpretation:

Surface coil MRI accurately stages many prostate cancer patients with elevated risk of extraprostatic disease. This mode of imaging may be reasonable at centres that do not have endorectal coil MRI.

What is the Optimal Staging Workup of Rectal Cancers?

Complete staging involves local staging and distant workup.

Distant workup

MDCT chest, abdomen and pelvis is the optimal method for distant workup. A systematic review comparing PETCT with CT found lack of data to support the use of FDG PET/CT in the routine staging of all patients diagnosed with primary colorectal cancers. Currently the role of PETCT is for detection of recurrence (particularly when CT is negative and CEA is rising) and for preoperative staging prior to metastectomy.

Local staging

The advent of high-resolution external phased array MRI has deeply impacted the local staging and treatment planning of rectal cancers. The standard surgical treatment for rectal cancers is total mesorectal

excision (TME) involving resection of the rectum with the mesorectal fat and the mesorectal fascia. This has reduced the incidence of local recurrences to below 10%. The advent of neo adjuvant chemo-radiation (NACT-RT) has further reduced the incidence of local recurrences.

High-resolution MR imaging helps select patients for upfront surgery versus NACT-RT by assessing the T stage,nodes and the circumferential resection margin (CRM) status. CRM is the shortest distance of the tumor/ perirectal node from mesorectal fascia (MRF) and is discussed in detail later.MRI cannot distinguish between T1 and T2 tumors, but has high accuracy for differentiating between T2 and T3 tumors and between T3 and T4 tumors.The overall sensitivity for T staging is 87% (specificity= 75%) while the specificity for prediction of CRM statuson MRI is 94%. The specificity of MRI for nodal status is 71%. Information from MRI also helps optimal radiotherapy planning and optimal surgical planning (abdomino-perinealresection or ultralow anterior resection, and sphincter saving surgery).

Endorectal Ultrasound (ERUS) is highly accurate for T staging of early tumors (T1 & T2) and is equivalent to other imaging methods for regional nodal metastases. ERUS is the method of choice to distinguish between T1 and T2 tumors whenendoscopic mucosal resection is contemplated. It can also help sphincter saving surgeries by depicting noninvolvement. For more advanced rectal cancers, MRI is mandatory to assess lateral spread that impacts treatment planning. ERUS is also not feasible in stenosing tumors.

CT & MDCT have been evaluated for local staging and are inferior to MRI in accuracy for all T stages, particularly to differentiate between advanced T3 and T4 stages. Although the MRF is visible clearly on MDCT, low accuracy for CRM prediction has been reported in lower third tumors. MDCT is also unable to predict the sphincter involvement accurately. However in the absence of MRI, CT can be used for local staging (MDCT preferred), but PETCT has no role in local staging of rectal and anal cancers.

Optimal workup-

1. Phased array external MRI Pelvis for local staging
2. Add ERUS in early tumor where local resection is being contemplated to differentiatebetween T1N0 and T2N+
3. MDCT chest and abdomen for distant workup.

Post NACT-RT imaging

MRI is the preferred method for restaging after neoadjuvant therapy.

Rectal MRI technique

Hardware& protocol

- Rectal MRI is performed with phased array surface coil; endorectal coil MRI is not recommended as it has a limited field of view (MRF may not be visible); is expensive and has reported 40% failed insertions in stenosing tumors.
- Different field strength magnets can be used with good results, but the imaging parameters have to be adjusted to get a good signal to noise ratio.

The minimum strength is a 1.0T scanner, but a 1.5T scanner is optimal and provideshigh resolutionimages. There is no evidence that a 3T magnet is superior to a 1.5 T magnet.

- Bowel preparation and rectal distension are not recommended routinely
- Spasmolytic use (buscopan) is optional.
- The present recommendation is to use T2W sequences in orthogonal planes to the tumor without fat saturation. Sagittal sequence is obtained first and used to plan coronal and oblique axial (perpendicular to long axis of rectum at the level of tumor).
- Diffusion weighted images are obtained along the same plane as the oblique axial; are not obligatory for primary staging, but useful for restaging after NACT-RT.
- Post gadolinium images are inappropriate (there is no data that use of post gadolinium images improves accuracy of T staging or CRM prediction).

II. What are the issues in local staging of the rectal cancer that every radiologist needs to know?

Following are the issues in rectal cancer local staging.

1. T stage.

Phased array MRI can display the mucosa, submucosa and muscularis.

- Tumor confined to the muscularis is T2 while tumor extending into the perirectal fat is T3.

- AJCC 7th edition staging subclassifies T3 tumors into —
  - T3a (<5mm spread from muscularispropria),
  - T3b (5-10mm from muscularispropria) and
  - T3c (> 10mm from muscularispropria).
- T1-T2 tumors with N0 status can be operated upfront. Regardless of N stage, T3a tumors have a reported 5 yr survival of 85%. T3b –T3c have a 5 yr survival of 54% and require intensive treatment with NACT-RT prior to TME surgery. T4 tumors require more radical surgery after NACT-RT.

2. Circumferential resection margin (CRM).

- CRM is the shortest distance of the disease from the mesorectal fascia
- CRM is not relevant to T1 and T2 tumors; CRM is measured in T3 and above tumors
- CRM is positive (+) when tumor/ node/deposit/ peritumoral stranding is located < 1mm from MRF (node is >3mm; deposit is <3mm in dimension)
- CRM is threatened when tumor/ node/deposit/ peritumoral stranding is located between 1-2mm of the MRF.
- CRM is negative if the above distance is > 2mm.
- In low rectal tumors, the CRM distance is measured from the tumor to thelevatorani
- A threatened or + CRM contraindicate upfront surgery and require NACT-RT with post-therapy restaging prior to surgery.

3. Nodal status

- Nodal size of limited criteria in detecting nodal metastases. 30-50% metastases in rectal cancer known to occur in nodes < 5mm
- Heterogeneity of nodes, irregular borders and nodes with similar signal intensity as tumor are suspicious.
- N1= 1-3 suspicious nodes, N2= 4 or more nodes
- Meta-analysis reports specificity of MRI for nodal metastases to be 71%.
- Pelvic sidewall nodes (iliac, obturator) need special mention as both radiotherapy and surgical planning may be altered.

4. Sphincter complex

- In low rectal tumors, the status of the sphincter complex needs mention.
- Coronal and axial scans are needed to evaluate the internal sphincter, external sphincter (puborectalis), intersphincteric plane, and levatorani.
- MRI can identify sphincter involvement in advanced tumors to select patients for NACT-RT. This could help increase sphincter preservation rate (by avoiding abdomino-perineal resection and offering an ultra-low anterior resection instead).

5. Distance from anal verge

This is identified on the sagittal image. The measurement should follow the curvature of the rectum in the form of successive straight line segments as in rigid sigmoidoscopy.

6. Extramural venous invasion (EMVI)

- It is an independent adverse prognostic factor
- It is the extension of tumor into blood vessels in the mesorectal fat beyond the tumor infiltrated muscularis
- Is relevant in T3 and above tumors
- EMVI is positive if the adjacent vessel shows tumor signal with/without border disruption OR is expanded.
- If EMVI is present and located<1mm of MRF , it indicates CRM + status

Checklist

- Location of tumor—
  a) upper, mid or low rectum; extension into anal canal—-
  b) The CC extent and
  c) distance from anal verge (always corroborate with clinical notes) &Optional- d) circumferential location
- T stage—
  - Look for the circularblack T2 signal of the intact muscularis; if involvedby tumor (replaced with hyperintense signal) =stage T2
  - If the dark rim is breached and extension into perirectal fat=stage T3.
  - Stranding into mesorectal fat could either be T3 or T2 with desmoplastic reaction. This should be reported as T2/T3.

- Optional—measure extramuralextension into perirectal fat beyond muscularis to sub classify into stages T3a-T3c (see above).
- Look for invasion of adjacent organs (bladder, ureter, prostate, uterus/vagina, sacrum) = stage T4 seen as loss of intervening fat plane and T2 hyperintensity in adjacent organ.

- CRM- mention a) if positive, threatened or negative b) reason for positivity (tumor/ node/ deposit/ stranding) c) shortest distance of tumor from MRF and the location.
- Sphincter status—External and internal sphincter, intersphincteric space, levatorani. In advanced disease, record extension beyond the pelvic floor into the ischiorectal fossa.
- Nodes- Number of perirectal nodes, extramesorectal (pelvic side wall) nodes
- Optional- EMVI –as 0 (absent) or present
- Others— Examine iliac vessels & muscles, bones (extensionupto pelvic sidewall is unresectable).

Response assessment after neoadjuvant therapy (with MRI)

- Look for intermediate signal of residual tumor and dark signal intensity of fibrosis to assess the extent of tumor regression.
- Rest of the features to be reported is same as in the pretreatment checklist.

Suggested reading

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Ann SurgOncol. 2012 ;19(7):2212-23.

Diagnostic accuracy of MRI for assessment of T category, lymph node metastases, and circumferential resection margin involvement in patients with rectal cancer: a systematic review and meta-analysis.

Al-Sukhni E, Milot L, Fruitman M, Beyene J, Victor JC, Schmocker S, Brown G, McLeod R, Kennedy E.

Abstract

Background:
Magnetic resonance imaging (MRI) is increasingly being used for rectal cancer staging. The purpose of this study was to determine the accuracy of phased array MRI for T category (T1-2 vs. T3-4), lymph node metastases, and circumferential resection margin (CRM) involvement in primary rectal cancer.

Methods:
Medline, Embase, and Cochrane databases were searched using combinations of keywords relating to rectal cancer and MRI. Reference lists of included articles were also searched by hand. Inclusion criteria were: (1) original article published January 2000-March 2011, (2) use of phased array coil MRI, (3) histopathology used as reference standard, and (4) raw data available to create 2□2 contingency tables. Patients who underwent preoperative long-course radiotherapy or chemo-radiotherapy were excluded. Two reviewers independently extracted data. Sensitivity, specificity, and diagnostic odds ratio were estimated for each

outcome using hierarchical summary receiver-operating characteristics and bivariate random effects modeling.

Results:

Twenty-one studies were included in the analysis. There was notable heterogeneity among studies. MRI specificity was significantly higher for CRM involvement [94%, 95% confidence interval (CI) 88-97] than for T category (75%, 95% CI 68-80) and lymph nodes (71%, 95% CI 59-81). There was no significant difference in sensitivity between the three elements as a result of wide overlapping CIs. Diagnostic odds ratio was significantly higher for CRM (56.1, 95% CI 15.3-205.8) than for lymph nodes (8.3, 95% CI 4.6-14.7) but did not differ significantly from T category (20.4, 95% CI 11.1-37.3).

Conclusions:

MRI has good accuracy for both CRM and T category and should be considered for preoperative rectal cancer staging. In contrast, lymph node assessment is poor on MRI.

Semin Ultrasound CT MR. 2005 Aug; 26(4):259-68.

Imaging for predicting the risk factors—the circumferential resection margin and nodal disease—of local recurrence in rectal cancer: a meta-analysis.

Lahaye MJ, Engelen SM, Nelemans PJ, Beets GL, van de Velde CJ, van Engelshoven JM, Beets-Tan RG.

Source
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Abstract

The aim of the present study was to conduct a meta-analysis of English literature on the accuracy of preoperative imaging in predicting the two most important risk factors for local recurrence in rectal cancer, the circumferential resection margin (CRM) and the nodal status (N-status).

Articles published between 1985 and August 2004 that report on the diagnostic accuracy of endoluminal ultrasound (EUS), computed tomography (CT), or magnetic resonance imaging (MRI) in the evaluation of lymph node involvement were included. A similar search was done for the assessment of the circumferential resection margin in rectal cancer in the period from January 1985 till January 2005.

The inclusion criteria were as follows: (1) more than 20 patients with histologically proven rectal cancer were included, (2) histology was used as the gold standard, and (3) results were given in a 2 x 2 contingency table or this table could otherwise be extracted from the article by two independent readers. Based on the results summary receiver operating characteristic (ROC) curves were constructed.

Only 7 articles matching inclusion criteria were found concerning the CRM.

The meta-analysis shows that MRI is rather accurate in diagnosing a close or involved CRM.

For nodal status 84 articles could be included.

The diagnostic odds ratio of EUS is estimated at 8.83. For MRI and CT, the diagnostic odds ratio are 6.53 and 5.86, respectively.

The results show that EUS is slightly, but not significantly, better than MRI or CT for identification of nodal disease. There is no significant difference between the different modalities with respect to staging nodal status.

At present, MRI is the only modality that predicts the circumferential resection margin with good accuracy, making it a good tool to identify high and low risk patients. Predicting the N-status remains a problem for the radiologist for every modality, although considering the new developments in MR imaging, this may change in the near future.

J ClinOncol. 2011 Oct 1;29(28):3753-60. doi: 10.1200/JCO.2011.34.9068. Epub 2011 Aug 29.

Magnetic resonance imaging-detected tumor response for locally advanced rectal cancer predicts survival outcomes: MERCURY experience.

Patel UB, Taylor F, Blomqvist L, George C, Evans H, Tekkis P, Quirke P, Sebag-Montefiore D, Moran B, Heald R, Guthrie A, Bees N, Swift I, Pennert K, Brown G.

Source

The Royal Marsden Hospital NHS Trust, Sutton, United Kingdom, SM2 5PT.

Abstract

Purpose:

To assess magnetic resonance imaging (MRI) and pathologic staging after neoadjuvant therapy for rectal cancer in a prospectively enrolled, multicenter study.

Methods:

In a prospective cohort study, 111 patients who had rectal cancer treated by neoadjuvant therapy were assessed for response by MRI and pathology staging by T, N and circumferential resection margin (CRM) status. Tumor regression grade (TRG) was also assessed by MRI. Overall survival (OS) was estimated by using the Kaplan-Meier product-limit method, and Cox proportional hazards models were used to determine associations between staging of good and poor responders on MRI or pathology and survival outcomes after controlling for patient characteristics.

Results:

On multivariate analysis, the MRI-assessed TRG (mrTRG) hazard ratios (HRs) were independently significant for survival (HR, 4.40; 95% CI, 1.65 to 11.7) and disease-free survival (DFS; HR, 3.28; 95% CI, 1.22 to 8.80). Five-year survival for poor mrTRG was 27% versus 72% (P = .001), and DFS for poor mrTRG was 31% versus 64% (P = .007). Preoperative MRI-predicted

CRM independently predicted local recurrence (LR; HR, 4.25; 95% CI, 1.45 to 12.51). Five-year survival for poor post-treatment pathologic T stage (ypT) was 39% versus 76% (P = .001); DFS for the same was 38% versus 84% (P = .001); and LR for the same was 27% versus 6% (P = .018). The 5-year survival for involved pCRM was 30% versus 59% (P = .001); DFS, 28 versus 62% (P = .02); and LR, 56% versus 10% (P = .001). Pathology node status did not predict outcomes.

Conclusion:

MRI assessment of TRG and CRM are imaging markers that predict survival outcomes for good and poor responders and provide an opportunity for the multidisciplinary team to offer additional treatment options before planning definitive surgery. Postoperative histopathology assessment of ypT and CRM but not post-treatment N status were important postsurgical predictors of outcome.2013 by American Society of Clinical Oncology

Preoperative Magnetic Resonance Imaging Assessment of Circumferential Resection Margin Predicts Disease-Free Survival and Local Recurrence: 5-Year Follow-Up Results of the MERCURY Study

Fiona G.M. Taylor, Philip Quirke, Richard J. Heald, Brendan J. Moran,Lennart Blomqvist, Ian R. Swift, David Sebag-Montefiore,Paris Tekkis andGina Brown

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ABSTRACT

Purpose

The prognostic relevance of preoperative high-resolution magnetic resonance imaging (MRI) assessment of circumferential resection margin (CRM) involvement is unknown. This follow-up study of 374 patients with rectal cancer reports the relationship between preoperative MRI assessment of CRM staging, American Joint Committee on Cancer (AJCC) TNM stage, and clinical variables with overall survival (OS), disease-free survival (DFS), and time to local recurrence (LR).

Patients and Methods

Patients underwent protocol high-resolution pelvic MRI. Tumor distance to the mesorectal fascia of d" 1 mm was recorded as an MRI-involved CRM. A Cox proportional hazards model was used in multivariate analysis to determine the relationship of MRI assessment of CRM to survivorship after adjusting for preoperative covariates.

Results

Surviving patients were followed for a median of 62 months. The 5-year OS was 62.2% in patients with MRI-clear CRM compared with 42.2% in patients with MRI-involved CRM with a hazard ratio (HR) of 1.97 (95% CI, 1.27 to 3.04; P < .01). The 5-year DFS was

67.2% (95% CI, 61.4% to 73%) for MRI-clear CRM compared with 47.3% (95% CI, 33.7% to 60.9%) for MRI-involved CRM with an HR of 1.65 (95% CI, 1.01 to 2.69; $P < .05$). Local recurrence HR for MRI-involved CRM was 3.50 (95% CI, 1.53 to 8.00; $P < .05$). MRI-involved CRM was the only preoperative staging parameter that remained significant for OS, DFS, and LR on multivariate analysis.

Conclusion

High-resolution MRI preoperative assessment of CRM status is superior to AJCC TNM–based criteria for assessing risk of LR, DFS, and OS. Furthermore, MRI CRM involvement is significantly associated with distant metastatic disease; therefore, colorectal cancer teams could intensify treatment and follow-up accordingly to improve survival outcomes.

Imaging of Common Extra-cranial Solid Tumors in Children

The common paediatric neoplasms are haematolymphoid malignancies followed by solid tumors like brain neoplsms, Neuroblastoma, Hepatoblastoma, Wilms' tumor, Rhabdomyosarcoma, etc. Imaging plays an important role in diagnosis, staging, risk stratification, response evaluation and follow up of most of the paediatric solid tumors. In this chapter we will discuss the role of imaging in Neuroblastoma, Hepatoblastoma and Wilms' tumor without going into the details of imaging characteristics of these tumors.

Being conscious about the use of ionizing radiation in children is essential. Measures should be taken to either avoid it completely like by using MRI or USG whenever possible or reduce the dose of radiation by "downsizing" the protocols to paediatric size, avoiding

plain and multiphase scan whenever possible and limiting the extent of the scan while performing a CT.

Imaging in neuroblastoma

Pretreatment evaluation

In a child with suspected Neuroblastoma, essential imaging includes cross sectional imaging like CT or MRI for loco-regional evaluation and MIBG for metastatic work-up. CT or MRI may be used depending upon availability of machines and the location of the primary tumor- MRI may display intra-spinal extension and marrow involvement better than CT. As of now there is no trial that recommends one over the other based on diagnostic accuracy.

The International Neuroblastoma Risk Group (INRG) Classification System published in 2009 uses imaging and other parameters like age, histopathology, grade of differentiation, n-myc amplification and chromosomal anomalies for risk stratification.[1] The staging system proposed by the task force is called as the International Neuroblastoma Risk Group Staging System (INRGSS).[2] The advantage of this system lies in it being a pre-surgical staging based on objective imaging criteria that can be applicable across the globe. The International Neuroblastoma Surgical Staging System is a post-surgical staging and INRGSS is not meant to replace it but to use it in pre-surgical staging.

Imaging is used to decide if the disease is L1, L2, M or MS as in table 1.

Table 1: INRGSS[2]	
Stage	**Description**
L1	Localized tumor not involving vital structures as defined by the list of IDRFs and confined to one body compartment.
L2	Loco regional * tumor with presence of one or more IDRF.
M	Distant metastatic disease ** (except stage MS)
MS	Metastatic disease in children younger than 547 days and metastases confined to skin, liver and/or bone marrow (< 10% of total nucleated cells on smears or biopsy).

* Locoregional : contiguous ipsilateral tumor within two body compartments.

** M: clearly separate lesions in two body compartments, non-regional lymphadenopathy, bone and/or marrow disease (not fitting into MS)

Image Define Risk Factors (IDRFs) are identified based on the location of primary and the vital structures in that anatomical compartment. Twenty such IDRFs have been identified and are mentioned in table 2.

Table 2 : Image defined Risk Factors (IDRFs)[2]	
Anatomic region	**Description of IDRF**
Multiple body compartments	Ipsilateral tumor extension within two body compartments (ie, neck and chest, chest and abdomen, or abdomen and pelvis)

Table 2 : Image defined Risk Factors (IDRFs)[2]	
Anatomic region	**Description of IDRF**
Neck	Tumor encasing carotid artery, vertebral artery, and/or internal jugular vein
	Tumor extending to skull base
	Tumor compressing trachea
Cervico-thoracic junction	Tumor encasing brachial plexus roots
	Tumor encasing subclavian vessels, vertebral artery, and/or carotid artery
	Tumor compressing trachea
Thorax	Tumor encasing aorta and/or major branches
	Tumor compressing trachea and/or principal bronchi
	Lower mediastinal tumor infiltrating costovertebral junction between T9 and T12 vertebral levels
Thoraco-abdominal	Tumor encasing aorta and/or vena cava
Abdomen and pelvis	Tumor infiltrating porta hepatis and/or hepatoduodenal ligament
	Tumor encasing branches of superior mesenteric artery at mesenteric root
	Tumor encasing origin of celiac axis and/or origin of superior mesenteric artery
	Tumor invading one or both renal pedicles

Table 2 : Image defined Risk Factors (IDRFs)[2]	
Anatomic region	**Description of IDRF**
	Tumor encasing aorta and/or vena cava Tumor encasing iliac vessels Pelvic tumor crossing sciatic notch
Intraspinal tumor extension	Intraspinal tumor extension (whatever the location) provided that more than one-third of spinal canal in axial plane is invaded, the perimedullary leptomeningeal spaces are not visible, or the spinal cord signal intensity is abnormal
Infiltration of adjacent organs and structures	Pericardium, diaphragm, kidney, liver, duodenopancreatic block, and Mesentery

The INRG task force has also specified the use of terminology like separation, contact, encasement, compression or infiltration of adjacent vital structures in a consensus report published in 2011.[3]

The investigation of choice for evaluation of metastatic disease is MIBG and bone marrow biopsy. ^{123}I is preferred over ^{131}I labelled MIBG because of higher sensitivity and lesser radiation dose to the patient. The guidelines of the task force for standardisation of MIBG patient preparation, technique and reporting have been published in 2010.[4] Use of scoring systems like SIOPEN or the Curie scoring system is recommended in evaluation of stage IV disease.

PET-CT can be used as a problem solving tool in non-MIBG avid primary and in equivocal or discrepant lesions on MIBG[5] Bone scan may be used when the primary is not MIBG avid; however it does not detect extra-skeletal abnormalities.

Response assessment

International Neuroblastoma Response Evaluation criteria have been established and are shown in table 3.

Table 3 : International Neuroblastoma Response Evaluation Criteria [6]

Response	Primary tumor	Metastatic disease
CR (complete response)	No tumour	No tumour, normal catecholamines
VGPR (very good partial response)	Decreased by 90%–99%	No tumour, normal catecholamines, improved 99mTc-MDP
PR (partial response)	Decreased by >50%	All sites decreased by >50%, no >1 positive bone marrow sites
MR (mixed response)	No new lesions; >50% decrease of any measurable lesion (primary or metastatic) metastatic) with 50% decrease in any other; 25% increase in any existing lesion	
NR (no response)	No new lesions, <50% decrease but <25% increase in any existing lesion	
PD (progressive disease)	Any new lesion, increase of any measurable lesion by >25%	

Follow up

There is no guideline or recommendation from the task force regarding follow up imaging, however, in general, patients with residual disease like in Stage IV require more frequent follow up till stability is shown on MIBG scan. Other methods of surveillance include serial urinary catecholamine levels.

Malignant paediatric liver tumors

Pretreatment evaluation

Ultrasound is usually the initial modality of choice for a suspected abdominal tumor. After a provisional diagnosis of liver tumor is established, it requires cross-sectional modality with triphasic scan for better characterization. While MRI would be preferred because of it being free of ionizing radiation, CT is often performed because of wider availability, shorter scan time, ease of sedation, ease of biopsy in the same setting (if required) and capacity to evaluate the chest for pulmonary metastases. It should be noted that multiphase scan should not be repeated for response evaluation or follow up unless it is essential for surgical planning.

A patient with hepatoblastoma may undergo upfront surgery if the disease is in an early stage or may be administered pre-operative chemotherapy, depending upon the protocol that is followed at one's institution. The PRETEXT (PRE treatment Tumor EXTension) staging system developed by SIOPEL for staging of hepatoblastoma can be used in evaluation of all

malignant liver tumors in children. The revised PRETEXT staging system has been published in 2007 by Roebuck et al.[7] This staging system is based on the number of contiguous hepatic sections that are free (table 4)and additional imaging criteria (table 5). For staging, the liver is divided into 4 sections. These sections are based on the Couinaud's segmental division of liver : segments II and III form the left lateral section, segments IVA and IV B form the left medial section, segments V and VIII form the right anterior section and the segments VI and VII constitute the right posterior section. Involvement of segment I (caudate lobe) is considered as at least stage II. Exophytic tumors are considered to occupy only the section(s) from which they originate.

Table 4: Pretext staging[7]

Pretext	Definition
I	One section is involved and three adjoining sections are free
II	One or two sections are involved, but two adjoining sections are free
III	Two or three sections are involved, and no two adjoining sections are free
IV	All four sections are involved

Table 5: Pretext: additional criteria[7]			
Criteria	**Symbol**	**Description**	**Comment**
Caudate lobe status	C	C0: doesn't involve caudate lobe C1 : involves caudate lobe	All C1 are at least stage II
Tumor focality	F	F 0: solitary tumor F1: two or more discrete tumors	
Portal vein status	P	P 0: No involvement of portal vein or its left or right branch P1 : involvement of left or right branch P2: involvement of main portal vein	Add suffix "a" if intravascular tumor is present eg : P2a
Hepatic vein / IVC involvement	V	V 0: no ivolvement of hepatic veins or IVC V1 : involvement of any one hepatic vin but not IVC V2: involvement of two hepatic veins but not IVC V3: involvement of all three hepatic veins and/or IVC	Add suffix "a" if intravascular tumor is present eg : P2a

Table 5: Pretext: additional criteria[7]			
Criteria	**Symbol**	**Description**	**Comment**
Extra-hepatic abdominal disease	E	E 0: No evidence of tumor spread in abdomen (except M or N) E1: Direct extension of tumor into adjacent organ or diaphragm E2 : discrete peritoneal nodule	Add suffix "a" if ascites is present eg : E1a or E0a
Tumor rupture or intraperitoneal haemorrhage	H	H1 : Imaging and clinical findings of intraperitoneal bleed	
Nodal metastases	N	N 0: No nodal metastases N1 : only abdominal nodal metastases N2 : any extra-abdominal nodal metastases	
Distant metastases	M	M 0: no metastases M1 :any metastases (except E and N)	

The SIOPEL does further risk stratification based on the staging system and tumor marker level. Table 6 shows an imaging check list for evaluation of liver tumors which encompasses all the features that need to be evaluated while reporting cases of hepatoblastoma.

Table 6: Imaging check list for liver tumors

Segments involved	**Number of adjacent segments free /pre-text stage**
Focality	Unifocal or multifocal or diffuse
Caudate lobe involvement	Yes/ No
Portal veins	Patent/thrombosed/compressed
Hepatic veins/IVC	Patent/thrombosed/compressed
Extra-hepatic extension	Hanging or infiltrating adjacent organs
Adenopathy	Yes/ No
Peritoneal disease	Yes/No
Metastases	Yes/No

Response assessment and follow up

The same staging system used after chemotherapy is referred to as POSTEXT staging (POST treatment Tumor EXTension). CT chest should be performed only if patient had lung metastases at baseline. After end of therapy, patients having elevated serum AFP levels at base line are best monitored by serial tumor marker evaluation. Imaging is recommended in case of rising titres.

Imaging in Wilm's Tumor

There are two approaches for management of Wilm's tumor. In North America children with renal tumors undergo upfront surgery, except in situations like bilateral tumors, tumor in a solitary or horseshoe kidney. Frank infiltration of adjacent organs, intra-atrial extension of tumor thrombus or extensive pulmonary metastases causing respiratory distress. The surgery is then followed by a stage and histopathology appropriate chemotherapy with or without radiotherapy. This is called as the NWTS (National Wilm's Tumor Study Group) approach. In Europe, almost all children with renal masses undergo pre-operative chemotherapy followed by surgery which is then followed by appropriate adjuvant therapy – chemotherapy with or without radiotherapy. This approach is called as the SIOP (International Society of Paediatric Oncology) approach. In SIOP approach, biopsy is not essential in children between 6 months to 5 years of age, but can be safely performed. Both approaches have comparable Overall Survival Rates.

The current staging of Wilm's tumor is a surgico-pathological staging system (both SIOP and NWTS). UKW3 trial is a randomized trial comparing the two approaches and has shown that SIOP approach has a favourable stage distribution.[8] Imaging can be used to select patients for either approach.[9] Cross sectional imaging helps in detecting findings where either surgery is contra-indicated (like in NWTS approach) or is likely to be difficult like large masses with/ without infiltration of adjacent organs or extensive adenopathy and in detecting stage IV disease- lung or liver

metastases. The check list for imaging is mentioned in table 7.

Table 7: Imaging check list for renal tumors[9]

Size	**Three dimensions and volume**
Local extent	Intra-capsular or not (if capsule seen). Any obvious infiltration of adjacent structures
Ureteric involvement	If present, extent of involvement
Vascular invasion	If present, extent: renal vein only or infra/intra/suprahepatic IVC and/or atrium
Peritoneal spread	Any obvious sign of rupture like haemorrhagic ascites or peritoneal deposits
Lymphadenopathy	If present, size and extent
Contralateral kidney	Normal or any obvious mass or any anomaly such as horseshoe kidney

Imaging can decide if the organ of origin of an abdominal tumor is kidney or not, however it cannot identify the histological types of paediatric renal tumors. A biopsy is considered safe if the patient is likely to undergo pre-operative chemotherapy (SIOP approach).[10] If the decision is made to do an upfront nephrectomy, a biopsy must be avoided as it would upstage the disease.

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