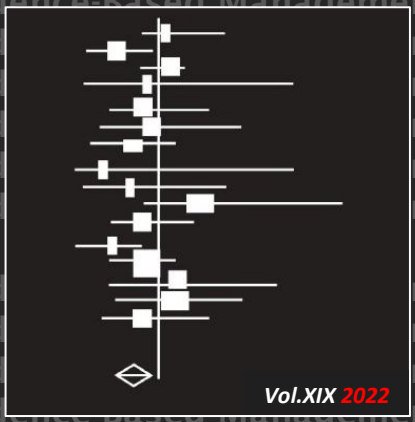
Evidence Based Management of Cancers in India-2022

Musculoskeletal Oncology
Updates from the meeting
On 19th & 20th February 2022



TATA MEMORIAL CENTRE

XX Annual Conference on
Evidence-Based Management of Cancers In India:
"Musculoskeletal Oncology"

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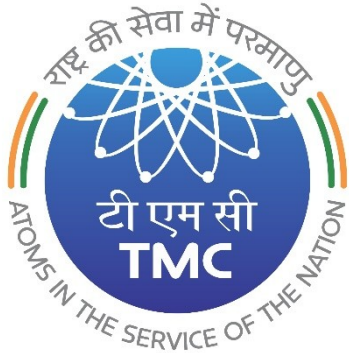

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Evidence Based Management of Cancers in India

Addendum-1
XX Annual Conference on Evidence Based Management of Cancers in India
"Musculoskeletal Oncology"
Updates from the meeting on 19th and 20th February 2022

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SARCOMA GENETICS

- The most common genes associated with germ line mutations in sarcomas are TP53, ATM, NF1, RB and BRCA2, arranged in decreasing incidence.

- International Sarcoma Kindred Study (ISKS) has reported a lower mean age of sarcoma diagnosis (41 versus 47 years) and multiple primaries in individuals with germ line mutations.

- Data from India (Sarin lab, ACTREC) is analogous to the global pattern of the genomic landscape in sarcomas with TP53 gene mutation (Li-Fraumeni syndrome) being the most common.

- When to employ genetic testing in patients with sarcomas?

  - Hereditary cancer syndromes - Genetic testing for germ line mutations should be employed in individuals with sarcomas who fulfill the classic Li-Fraumeni (LF) syndrome and LF like syndromes.

  - Sporadic cancers – Considering the low incidence of germ line mutations in sporadic sarcomas, genetic testing needs to be employed on case-to-case basis with the most important factor being young age. Patients diagnosed of sarcoma with history of malignancy in a close family member have a distinct possibility of genetic mutation in the known genes.

- The way ahead is to develop targeted molecules against actionable mutations to modify the expression of such gene mutations, providing novel prophylactic therapies for families with such germ line mutations.

DIAGNOSIS AND STAGING

- In sarcomas, Magnetic Resonance Imaging (MRI) is the gold standard for local imaging, while Computed Tomography (CT) chest is the standard for detecting lung metastases.

- Positron Emission Tomography-Computed Tomography (PET/CT) is superior in detecting skeletal/nodal/visceral metastases in sarcomas, as compared to bone scan and whole-body MRI.

- PET-CT vs. Bone scan – pros and cons

  - PET-CT has a higher sensitivity in detecting skeletal metastases than bone scan (higher incremental value in Ewing's sarcoma than in osteosarcoma).

  - Bone scan may miss out in detection of physeal plate metastases (False negative), while they are more likely to be appreciated in PET- CT.

  - PET-CT has a high sensitivity in detecting marrow metastases in Ewing's sarcoma (negligible false negativity rate), hence obviates the need of a bone marrow biopsy when PET CT is negative for bone marrow disease.

- PET-CT vs. Whole body (WB) MRI – pros and cons

  - PET-CT is not a good modality to differentiate between reconverted marrow and bone marrow metastases and also may miss small marrow metastases (false negative)

  - MRI is more sensitive for brain and marrow metastases; however, the overall incremental value is questionable.

- Small lung metastases are likely to be missed in WB-MRI.
- Lymph nodal disease is equally detected by PET-CT and WB-MRI.
- Due to challenges in acquisition and interpretation (variations between centers) and the current exorbitant cost of WB-MRI, there is very limited acceptance of the same, despite overall similar accuracy in staging when comparing PET-CT and WB-MRI.

- PET-MR – Though PET-MR is proposed to be a promising investigation for combined local and systemic staging, currently there is no positive data to support its use. Also, PET-MR may not be necessarily superior to PET-CT and other conventional imaging modalities, despite the advantages of the PET and MR individually.
  - MRI and PET (without CT) are not sensitive for lung metastases.
  - Long acquisition time, prohibitively high cost and accessibility are major concerns.

- Role of PET-CT in systemic staging is
  - Chondrosarcoma – can be avoided considering the small incidence of isolated bone metastases. CT chest is optimal modality for systemic staging
  - Soft tissue sarcoma – has a minimal incremental value over CT chest. PET-CT may add value in certain cases - occult bone metastasis/muscular metastasis, missed visceral disease on CT/MRI, soft tissue metastases outside the field of conventional imaging.

CURRENT AJCC CLASSIFICATION: IMPACT AND LACUNAE

8th edition AJCC classification has added location of the tumor in staging of bone and soft-tissue sarcomas along with other factors such as size, grade, lymph nodal metastases and distant metastases.

Bone sarcomas

- Grade - The revised subgroups are grade 1 and grade 2/3. However, grade 4 has been removed.
- Size –8 cm is used as a threshold to dichotomous extremity sarcomas based on size, while T3 includes those with skip metastases.
- Though not included as a factor for staging, studies have reported worse survival outcomes with venous thrombus/vascular invasion, despite similar stages.
- Impact of changes and lacunae
  - Positives – Anatomical location added as a factor, as sarcomas of different locations essentially have varied outcomes, despite similarity in other factors.
  - Negatives – The new sub grouping of grades may not be relevant for chondrosarcomas as there is no difference in outcome between grade 1 & 2 and there is significant difference between grade 3 & 4.

Soft Tissue Sarcomas

- Sub grouping on the basis of size in STS depends on the tumor location.
- Depth as a factor in staging has been removed.
- Impact of changes and lacunae
  - Positives – Anatomical location has been added as a factor.
  - Negatives – Considering the heterogeneity of STS, the current staging does not still stratify between the many histologies. Several studies have reported that size as a continuous variable is more relevant and impactful in STS, with a 3-5% increase in death with every increase of a centimeter in size. The current AJCC may be improperly classifying patients with nodal disease with Stage IV, though their outcome is distinctly better than other stage IV provided a lymph nodal dissection has been performed. Depth has been abolished as a factor. This may not have an impact on low grade tumors; however, outcomes in superficial and deep high grades are considerably different.

Overall, the 8th edition AJCC staging classification is complex and will need further modifications. Though the use of AJCC staging in sarcomas has been questioned by many researchers, there is still no data to abolish the use of the same in current practice.

CURRENT ROLE OF MOLECULAR DIAGNOSTICS

- Advantages with advanced molecular testing
  - Confirm diagnosis
  - Escalate therapy / de-escalate therapy – avoiding mutilating surgery; chemo resistant biology
  - Actionable mutations
  - Novel therapies
  - Estimating prognosis better and disease biology

- When to do molecular testing?
  - Unrealistic to do in all patients.
  - To be considered in clinical trials so as to capture rare actionable mutations with a known denominator and when the therapeutic implications is realistic in the non-trial setting with a high incidence of a particular genetic alteration.
  - May not be beneficial for an individual patient, but will propel science forwards!

- Way forward
  - Centralize genomic testing so as to reduce the cost
  - Being pragmatic in choosing the relevant panels for sarcomas

OSTEOGENIC SARCOMA

- There is a limited role of newer agents in osteogenic sarcoma.
- While treating osteogenic sarcoma in the elderly, one has to keep in mind the Quality of life, patient-reported outcomes, and multimodality geriatric assessment to minimize toxicity and balance survival outcomes.
- Overall survival is dismal in patients with recurrent disease. Survival is better in patients with asymptomatic relapse and after 18 months of treatment.
- Surgery remains the mainstay at recurrence, however high dose definitive radiation can be tried in patients not amenable to surgical resection.
- There is no consensus on the chemotherapy regimen and when to use it. Multiagent is slightly better than a single drug.

EWINGS SARCOMA

- Published studies have reported a marginally better local control with proton therapy as compared to photon therapy and a significant benefit in reducing toxicities.
- Various disease characteristics are factored in while selecting patients with upfront metastatic ES for curative intent.
  - Age - >14 years confers a worse prognosis
  - Volume - >200ml has a worse prognosis
  - Locations – did not have an impact in metastatic sarcomas
  - Isolated lung metastases have much better survival than bone marrow and skeletal metastases. Also, multi-system metastases have a bad prognosis
  - Poor histological response to induction chemotherapy is a poor prognostic factor.

SOFT TISSUE SARCOMAS

- The benefit of chemotherapy in STS is minimal, 4% at 10 years
- Of all different histologies of STS, the so-called chemo sensitive histologies constitutes <30% of tumors, so chemotherapy should be an exception
- Data is uncertain on chemotherapy in STS, long term toxicities should be borne in mind (fertility, cardiac/ renal toxicity and secondary malignancy), neo-adjuvant treatment can lead to delay in surgery.
- MSKCC prediction tool for LR prediction and PERSARC app can be tools to predict risk of failures with or without use of radiation and chemotherapy
- Targeted therapy in soft tissue sarcomas
  - NTRK fusions are rare events but their inhibitors have shown high response rates regardless of tumor types in early phase trials
  - EZH2 inhibitor tazemetostat has shown activity in epithelioid sarcoma.
  - Antiangiogenic TKI has shown interesting activity and improved overall survival in ASPS and solitary fibrous tumors.
  - ALK inhibitor crizotinib and alectinib have shown activity in inflammatory myofibroblastic tumors.
- Immunotherapy
  - Unspecific immunotherapy has little evidence for efficacy.

- Immune checkpoint inhibitors have responses in a limited number of patients.
- In a limited-resource setting, immune checkpoint inhibits can be used for a limited period of time.

EXTRA-ABDOMINAL DESMOID TUMORS

- Active surveillance is the standard of care.
- Surgery may be reserved for progressive disease after failed medical management and in case of limited morbidity and functional loss.
- Sorafenib 400mg OD has shown increased response rate and progression-free survival compared to placebo.
- Cytotoxic chemotherapy (Mtx/Vinblastine or pegylated liposomal doxorubicin) can be reserved for patients with rapidly progressive tumors or life-threatening emergencies.
- Possible indications for radiotherapy in extra-abdominal desmoid tumors -
  - an unresectable tumor (critical anatomical location where surgery would involve prohibitive risk or functional impairment).
  - at recurrence or progression or after multiple failed lines of treatment.
  - where salvage surgery could result in significant morbidity.
- Cryoablation is safe and can be done on day-care basis in patients progressing on medical treatment.
- RFA and magnetic resonance-guided focused ultrasound treatment are possible non - invasive options in the treatment of extra-abdominal desmoid tumors.

MINIMALLY INVASIVE TREATMENTS

- Radio frequency ablation (RFA) requires a delicate balance in between ablation and damage to adjoining growth plate/ articular cartilage in benign osseous tumors. RFA can be an alternative to surgery in <2.5cm well corticated lesions. Weight bearing joints have a risk of collapse and should be dealt with caution.

- RFA is safe and effective, with a low risk of recurrence and complications. We should always aim for complete ablation of lesion; a delicate balance needs to be kept between tumor ablation and articular damage. Debulking/ partial ablation can be done for lesions having risk of major complications or in close proximity to vital structures. FDG PET can be used for assessing the response.

- Thermo ablation is efficient for small pulmonary metastatic nodules 2-3 cm, and it is yet unclear whether any technique (Sx/ RFA/SBRT) is superior to the other

- SABR (stereotactic radio-surgery) has low morbidity, is cost effective, may invoke systemic immunity and is a viable option in pulmonary metastasis.

TECHNOLOGICAL ADVANCEMENTS

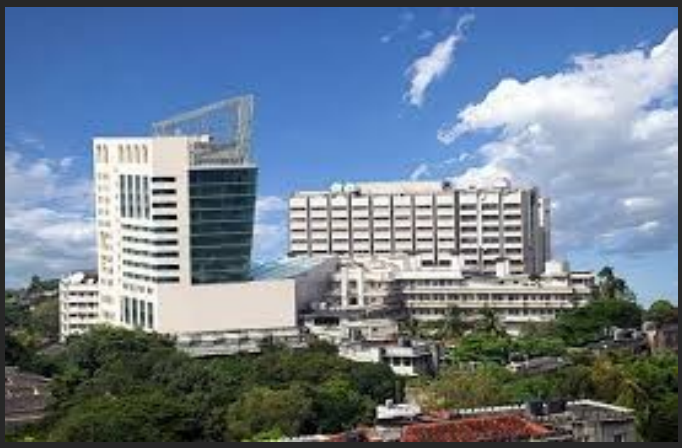
- Computer Navigation in the pelvis can help in reduced complications, improved function, increased chance of achieving better margins, reduced risk of locally recurrent disease

- Advantages of particle ions - enhanced local control, superior normal tissue sparing and dose escalation to the tumor as compared to photons. Superior functional outcomes compared to surgery needs further study. Toxicities related to particle ions are increased fracture rate and a higher risk of femoral head necrosis. A major disadvantage of particle ion therapy is limited access.

- Percutaneous cryoablation for extra abdominal desmoid tumors is safe with low complication rate and no documented long term toxicities. Treatment can be staged to improve safety and response. Evidence suggests durable short to medium term tumor response and benefit to the patient in terms of disease control, pain and QoL.

- Innervated muscle flaps in reconstruction after excision of limb sarcomas gives better gait profile score, walking velocity and step time symmetry ratio. Patients can complete activities of daily living without affecting gait velocity. PROMS (Patient related outcome measures) using TESS show significant difference with such functional reconstruction as compared to nonfunctional reconstruction.

- Vascularized epiphyseal transfers (VEFT) for reconstruction after pediatric limb sarcomas harvested on anterior tibial artery and anastomosed in a reverse flow fashion have shown superior outcomes and a reduced recipient site complication profile. However, based on the limited experience, the overall complications rate of VEFT remains high and harvest of proximal fibula may result in permanent peroneal nerve palsy. Lower extremity reconstruction is more prone to complications such as fracture and non-union.



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