2017 Sarcoma Year Review

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Are outcomes of osteosarcoma in Indian patients any different?

Most large series of osteosarcoma include Caucasian patients. This large retrospective study of 853 osteosarcoma patients from Tata Memorial Centre, Mumbai [1] analyzed their data to ask, if our patients do any differently than the rest of the world. The major difference is the lack of use of high dose methotrexate in this subset because of logistical constraints. Instead most patients received 2 cycles each of cisplatin/doxorubicin, ifosfamide/doxorubicin in the neoadjuvant setting, followed by 4 cycles of cisplatin/ifosfamide in the adjuvant setting. The 5 year overall survival for the entire cohort was 49 % and event free survival was 42%, while the non-metastatic ones had an OS of 53% and EFS of 47 % at 5 years. Eighteen (9%) patients developed local recurrence, 311 developed metastasis while, 47 developed both. Site of tumor, type of surgery and chemotherapy induced necrosis were significant even on multivariate analysis. Interestingly 70 % patients in this series were male, likely revealing a referral bias favoring the male in the subcontinent. The 11 % rate of metastasis is also a selection bias as only patients treated with a curative intent were analyzed n the study. One fourth patients underwent an amputation suggesting delayed referral to specialist sarcoma centers and / or inadvertent prior intervention. Ninety percent of tumors were over 8 cm. The overall survival has been lower than a lot of other Caucasian reports. Although the best results from the non HDMTX based chemotherapy report survival of up to 79% in a limited cohort of 72 patients, the change and intensification of therapy at TMC, Mumbai in 2012 does not seem to have significantly improved survival outcomes. The large tumor sizes may have a larger negative influence.

Predictors of venous thromboembolism in patients with bone sarcoma

Venous thromboembolism is associated with both orthopedic surgery and cancer. The incidence is estimated to be 0.6 to 15 % with the use mechanical and or chemical prophylaxis. Prophylactic anticoagulation to decrease the morn=morbidity and mortality associated with VTE can itself lead to bleeding and wound complications especially in patients with perioperative radiation and large volume resections. Current recommendations are unclear about the choice or duration of the chemical prophylaxis. These recommendations are in patients undergoing knee or hip arthroplasty or hip fracture fixation. Kaiser et al in this study analyse the rate of VTE, the risk factors associated with VTE and discuss complications associated with prophylactic anticoagulation in patients with primary bone sarcoma. This retrospective study [2] in adult patients treated for sarcoma over 25 years were identified for radio-graphically confirmed VTE or pulmonary embolism occurring within 90 days of index surgery. Various patient characteristics, preoperative clinical variables and treatment variables were used for analysis. Bi-variate logistic regression was used to estimate a crude odds ratio, l significant and non collinear factors then underwent a backward elimination step-wise regression to calculate adjusted odds ratio. Out of 379 patients analyzed, 100 received no prophylaxis and 279 did. Two of those 100, while 19 of the 279 who received prophylaxis developed VTE (p= 0.012). Median time to event was 27 days. Initial bi-variate analysis showed pre=operative white blood cell count, preoperative hematocrit, estimated blood loss, post-operative wound infection, wound complications, additional surgery and multi-drug chemoprophylaxis. High pre-operative white blood cell count, post-operative wound complications were independent risk factors at final analysis. The risk of wound complications increased significantly in those who received chemical prophylaxis. Although retrospective nature of the data and that sub-clinical events of VTE were missed and prophylactic therapy was heterogeneous, the data resembles real life scenario and provides valuable data in bone sarcoma patients. It is important to note that wound complications often necessitates repeated surgery, bed rest or VAC therapy which worsen the risk of VTE. Since chemoprophylaxis worsens the risk of wound complications, we need to ask if we causing undue harm in a subset of patients. This is in the light of some studies that suggest that sites other than pelvis and hip may not have sufficient risk of VTE to warrant prophylaxis. To reduce the risk further, would mechanical devices with low risk aspirin suffice to optimally reduce VTE risk while also keeping risk of wound complications low? In conclusion prospective studies are needed to accurately stratify risk in this patient population for optimal and safe use of chemoprophylaxis. Aggressive prophylaxis may counter intuitively

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increase the risk of thromboembolic events.

Individualized risk assessment for local recurrence and distant metastases for extremity soft tissue sarcoma

Limb salvage surgery with radiation in adjuvant or neoadjuvant form is the standard of care for most patients with extremity soft tissue sarcoma (STS). Despite high rates of limb salvage, local recurrence and distant metastasis remain real concerns. Patient's prognosis is determined by disease related variables which are fixed at diagnosis and treatment related factors which are modifiable. Surgical resection margins and use of radiation and chemotherapy are the only modifiable factors that can influence outcome. Small heterogeneous study populations are misleading to help predict outcomes in an individual patient. For instance would the predicted LR (local recurrence) and OS (overall survival) be the same in a 25 year old male with positive margin excision for myxo-fibrosarcoma vs a 65 year female with a large deep leiomyosarcoma? We know that LR risk is prohibitively high in the former, while metastatic risk is high in the latter. Willeumier et al (3) present a study where a multi-state model is used to predict LR and survival in a large population with high grade extremity STS. A multi-state model is a model for time to event data where all individuals start with one state (eg, surgery) and go on to develop one or more states of LR, metastasis or both of the above. The probability of getting an event are based on transition hazards as measured by a Cox model. These models can be used with 2 aims, one to gain biological insight into the disease process and the other to help predict outcomes from the training set which may impact treatment decisions. The results are provided in the form of stacked charts acting as a visual aid (shown below). The probabilities of having a recurrence or a metastasis change with time and with treatment evolution. Two interesting observations which need validation with prospective studies, are that neo adjuvant radiation is associated not only with decreased LR as compared to adjuvant radiation but also associated with better survival. The strengths of the study are the large cohort of high grade extremity STS and the use of multi-state model to assess probability of clinical future events. AJCC and other staging systems provide prognostic estimates for group of patients, this study introduces the possibility of allowing treatment to be tailored to individuals. The retrospective design, selection bias, multi-centre data are weaknesses. The authors mention that a web based application will further enable personalised care, however the model needs external validation from multiple centres.

Latest Guidelines and Reviews:

Few good reviews and guidelines were published this year. The National Comprehensive Cancer Network published their guidelines for Ewings sarcoma which provides a step wise evidence based algorithmic approach to Ewing sarcoma patients [4]. An excellent review on advancement in management of paediatric bone sarcoma was published by Grohar et al [5]. Details of most recent updates in literature are synthesized together with excellent commentary by authors. However probably one of the most important paper this year is published in Cancer Journal [5]. This paper by Reed et al [6] tries to establish a consensus statement for various pediatric bone sarcoma. A multidisciplinary approach involving the experienced orthopedists, radiotherapists, radiologists, pathologists, and oncologists was followed to develop a detailed management approach. The entire paper is put up in a question answer format which is includes clinically relevant question and proposed answers through consensus among all the disciplines including taking into account the current evidence. This seemed to a very interesting approach to answer locally relevant questions and also help prioritize research and resources in areas identified to be most promising. The article itself is a delight to read and similar consensus building exercises can be a part of orthopaedic oncology network in our country too.

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