

Dear Editor,

We have made all changes in Manuscript ID # World Journal of Orthopedics: 26842 entitled “**Management of Ewing sarcoma family of tumors: current scenario and unmet need**” as suggested by reviewers and editorial members. Please find here the point wise response sheet along with revised article. **All changes are highlighted in yellow.**

Editorial comments

Comments 1: Please offer signed pdf file. Thank you! (For conflicts of interest statement)

Response: the same has been provided with revised manuscript.

Comments 2: Please offer the audio core tip.

Response: the same has been provided with the revised manuscript.

Reviewer #1

Comment: The Table 1 should include information in which the readers could understand conceptual shift from adjuvant to neoadjuvant settings.

Response: We would like to mention that all the chemotherapy trials or studies mentioned in Table 1 include neoadjuvant chemotherapy setting. The usual mode of treatment is neoadjuvant chemotherapy followed-by local treatment (in terms of surgery and/or radiotherapy) and further adjuvant chemotherapy. High dose chemotherapy with autologous stem cell rescue is used in case of advanced disease in addition to the neoadjuvant chemotherapy and local therapy. A foot note has been added to Table 1 stating the aforementioned fact.

Reviewer #2

Comment: This review provides a very updated and comprehensive evaluation of the incidence of Ewing sarcoma and associated tumors and complications, the new avenues

available in terms of therapeutic approaches, including the short and long-term beneficial effect of new chemotherapeutic agents, and surgical removal of single metastasis and the prognosis in terms of life expectancy and quality of life.

Response: We are very thankful and obliged by the reviewer's comment.

Reviewer #3

Comment: The paper is about an important topic. It is well written and balanced. I believe it will be of interest for the Journal's readership.

Response: We are very thankful and obliged by the reviewer's comment.

Reviewer #4

Comments 1: "... the focus is now on to minimize toxicities –like chemotherapy related, radiotherapy related..." What about fertility preservation in these adolescents and young adults? This large field is completely overlooked. What are the consequences of chemotherapy on the gonads and the suggested modalities to minimize these remote and devastating side effects?

Response: The reviewer has pointed an important and relevant issue about long-term toxicity in cancer treatment and its prevention, especially fertility issue. The same has been addressed in the revised manuscript (page 16 line: 10-23 & page 17 line: 1-20).

Comments 2: The possibility of ovariopexy before pelvic irradiation needs to be discussed.

Response: Ovariopexy or ovarian transposition is definitely an effective method to preserve ovarian function in case of pelvic irradiation in ESFT. Ovariopexy should be considered in patients with pelvic ESFT where radiation is required as part of the local treatment modality and the patient need fertility preservation (page 17 line: 11-15)

Comments 3: Does Ewing Sarcoma metastasize to the gonads? It is relevant for ovarian cryopreservation.

Response: The reviewer has pointed yet another interesting and important issue. Primary ovarian ESFT, though very infrequent, has been reported in literature. Metastasis to ovary in ESFT is another very rare phenomenon. We found only three cases where metastasis to ovary from a primary ESFT of distant location has been reported in literature (Page 18, line: 1-2, Ref no 85-87). Both of the prior mentioned scenario is vital and relevant for ovarian cryopreservation and should be given due consideration.

Comment 4: What about minimizing the gonadotoxic effect of combination chemotherapy, using GnRHa Co-treatment?

Response: GnRH-a co-treatment has some protective role in chemotherapy induced gonadotoxicity. The same has been addressed in revised manuscript (page no 17, line: 16-20).

Comment 5: Please define tumor "resectability".

Response: By using the term “resectability”, we want to mean that whenever a non-mutilating surgery can be done with preservation of a functional organ and negative oncological margin, one should try to do surgery as local treatment modality after neoadjuvant chemotherapy in ESFT. It depends on tumor site, size, age of the patient and experience of the surgeon and the treating institution.

Sincerely

Dr. Bivas Biswas