

**A retrospective study of local relapse after high grade osteosarcoma**

<b>Sponsor's Name</b>	EMSOS
<b>Study Number/Version/Date:</b>	vers. Draft 29 June 2019
<b>Development Phase:</b>	Obervational
<b>Type:</b>	Retrospective and Prospective

DRAFT

## **Protocol Synopsis**

### **Background**

Treatment of osteosarcoma has evolved in the last 40 years: with the introduction of neo-adjuvant chemotherapy, 5-year survival rates for patients affected by high-grade osteosarcoma have improved from 15% to more than 70%<sup>1-6</sup>.

To date, many osteosarcomas are cured by multiagent chemotherapy and surgery, but a significant number still relapse: after treatment of the primary osteosarcoma, 40% to 50% of patients will develop local relapse (LR), distant metastases (DM) or both<sup>7-15</sup>.

Few analyses in literature report on locally recurrent disease as it remains uncommon, with LR rate ranging from 4% to 10%<sup>10-17</sup>. Prognosis of patients experiencing LR is generally considered poor, however most data available do not provide sufficient details<sup>7,8,15</sup>. DM are such an overriding determinant of survival, and LR is so infrequent, that it is difficult to study local recurrence as an independent variable<sup>15-22</sup>.

Also, in case of LR, while the importance of achieving a second surgical complete remission is well known, the role of second line chemotherapy is under discussion, with a mono-institutional experience showing no advantage in of chemotherapy after local relapse<sup>23</sup>

## **Objective**

Aim of this study is to analyse the modalities of diagnosis of LR in high-grade osteosarcoma, pattern of recurrence, treatment of LR and factors influencing post-LR survival (PLRS) focusing on the role of second line chemotherapy, margins and type of surgery

## **Inclusion criteria**

- Patients who experienced LR as first event of recurrence after treatment for localized high-grade osteosarcoma

AND

- Information available (date of primary tumor first surgery, date of LR, modality of LR diagnosis (clinical suspect or imaging), presence or absence of DM at LR diagnosis, type of treatment after LR, date of surgical complete remission after LR (CR2)<sup>o</sup>, surgical margins, date and status at last follow-up.

<sup>o</sup>CR2: removal of all evident metastatic disease, with no tumor tissue at resection margins on histologic examination.

## **Exclusion criteria**

- Cases of LR demonstrated after > 3 months after metastatic disease

**Age group:** patients will grouped as follow: pediatric (0-15 years), adolescent and young adults (AYA) (16-29 years) and adults (30 years or older).

---

## **REFERENCES**

---

- <sup>1</sup> Jaffe N. Recent advances in the chemotherapy of metastatic osteogenic sarcoma. *Cancer* 1972; 30:1627–31.
- <sup>2</sup> Meyers PA, Heller G, Healey J, et al. Chemotherapy for nonmetastatic osteogenic sarcoma: the Memorial Sloan-Kettering experience. *J Clin Oncol* 1992; 10:5–15.
- <sup>3</sup> Hagleitner MM, de Bont ES, Te Loo DM. Survival trends and long-term toxicity in pediatric patients with osteosarcoma. *Sarcoma* 2012; 2012:636405.
- <sup>4</sup> Bacci G, Briccoli A, Ferrari S, et al. Neoadjuvant chemotherapy for osteosarcoma of the extremity: long-term results of the Rizzoli's 4th protocol. *Eur J Cancer* 2001; 37:2030–9.
- <sup>5</sup> Wilkins RM, Cullen JW, Odom L, et al. Superior survival in treatment of primary nonmetastatic pediatric osteosarcoma of the extremity. *Ann Surg Oncol* 2003; 10:498–507.
- <sup>6</sup> Zalupski MM, Rankin C, Ryan JR, et al. Adjuvant therapy of osteosarcoma--a phase II trial: Southwest Oncology Group study 9139. *Cancer* 2004; 100:818–25.
- <sup>7</sup> Nathan SS, Gorlick R, Bukata S, et al. Treatment algorithm for locally recurrent osteosarcoma based on local disease-free interval and the presence of lung metastasis. *Cancer* 2006; 107:1607-16.
- <sup>8</sup> Bacci G, Forni C, Longhi A, et al. Local Recurrence and Local Control of Non-Metastatic Osteosarcoma of the Extremities: A 27-Year Experience in a Single Institution. *Journal of Surgical Oncology* 2007; 96:118-123.
- <sup>9</sup> Bacci G, Ferrari S, Mercuri M, et al. Predictive factors for local recurrence in osteosarcoma: 540 patients with extremity tumors followed for minimum 2.5 years after neoadjuvant chemotherapy. *Acta Orthop Scand* 1998; 69: 230-236.
- <sup>10</sup> Weeden S, Grimer RJ, Cannon SR, et al. The effect of local recurrence on survival in resected osteosarcoma. *Eur J Cancer* 2001; 37:39-46.

- <sup>11</sup> Bacci G, Ferrari S, Longhi A, et al. Pattern of relapse in patients with osteosarcoma of the extremities treated with neoadjuvant chemotherapy. *Eur J Cancer* 2001; 37:32-8.
- <sup>12</sup> Duffaud F, Digue L, Mercier C, et al. Recurrences following primary osteosarcoma in adolescents and adults previously treated with chemotherapy. *Eur J Cancer* 2003; 39:2050-7.
- <sup>13</sup> Puri A, Giulia A, Hawaldar R, Ranganathan P, Badwe RA. Does intensity of surveillance affect survival after surgery for sarcomas? Results of randomized noninferiority trial. *Clin Orthop Relat Res.* 2014; 472:1568-75.
- <sup>14</sup> Goorin AM, Delorey MJ, Lack EE, et al. Prognostic significance of complete surgical resection of pulmonary metastases in patients with osteogenic sarcoma: Analysis of 32 patients. *J Clin Oncol* 1984; 2:425-31.
- <sup>15</sup> Kempf-Bielack B, Bielak S, Jurgens H, et al. Osteosarcoma Relapse After Combined Modality Therapy: An Analysis of Unselected Patients in the Cooperative Osteosarcoma Study Group (COSS). *J Clin Oncol* 2005; 23:559-68.
- <sup>16</sup> Bacci G, Longhi A, Cesari M, Versari M, Bertoni F. Influence of local recurrence on survival in patients with extremity osteosarcoma treated with neoadjuvant chemotherapy: the experience of a single institution with 44 patients. *Cancer* 2006; 106:2701–6.
- <sup>17</sup> Grimer RJ, Taminiu AM, Cannon SR; Surgical Subcommittee of the European Osteosarcoma Intergroup. Surgical outcomes in osteosarcoma. *J Bone Joint Surg Br.* 2002; 84:395–400.
- <sup>18</sup> Aljubran AH, Griffin A, Pintilie M, Blackstein M. Osteosarcoma in adolescents and adults: survival analysis with and without lung metastases. *Ann Oncol* 2009; 20:1136–41.
- <sup>19</sup> Casali PG, Bielack S, Abecassis N, et al. Bone sarcomas: ESMO–PaedCan–EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2018; 29:79–95.

- <sup>20</sup> Gerrand C, Athanasou N, Brennan B et al. British Sarcoma Group: UK guidelines for the management of bone sarcomas. *Clin Sarcoma Res* 2016; 6:7.
- <sup>21</sup> Grimer RJ, Sommerville S, Warnock D, Carter S, Tillman R, Abudu A, Spooner D. Management and outcome after local recurrence of osteosarcoma. *Eur J Cancer* 2005; 41:578–83.
- <sup>22</sup> Ferrari S, Briccoli A, Mercuri M, et al: Postrelapse survival in osteosarcoma of the extremities: Prognostic factors for long-term survival. *J Clin Oncol* 2003; 21:710-5.
- <sup>23</sup> Palmerini E, Torricelli E, Cascinu S, et al: Is there a role for chemotherapy after local relapse in high-grade osteosarcoma. *Pediatr Blood Cancer*. 2019 Aug;66(8):e27792.

DRAFT