Postoperative Radiation Therapy in Patients with Extracranial Chondrosarcoma: A Joint Study of the French Sarcoma Group and Rare Cancer Network

Mario Terlizzi, Cécile Le Pechoux, Sébastien Salas, Etienne Rapeaud, Delphine Lerouge, Marie P. Sunyach, Guillaume Vogin, Claudio V. Sole, Thomas Zilli, Myroslav Lutsyk, et al.

Version of Record: https://www.sciencedirect.com/science/article/pii/S0360301620309858
Manuscript_32650810225123d10199c17074853d79

Postoperative radiotherapy in patients with extracranial chondrosarcoma, a joint study of the French Sarcoma Group and Rare Cancer Network

Short running title: **Radiotherapy in extracranial chondrosarcoma**

M. Terlizzi MD [1], C. Le Pechoux MD PhD[2], S. Salas MD PhD[3], E. Rapeaud MD[4], D. Lerouge MD[4], M. P. Sunyach MD [5], G. Vogin MD PhD[6], C. V. Sole MD PhD[7], T. Zilli MD PhD[8], M. Lutsyk MD[9], A. Mampuya MD[10], F. A. Calvo MD[11], J. Attal MD[12], V. Karahissarlian MD[5], B. De Bari MD[13], M. Ozsahin MD PhD[10], F. Baumard MSc[14], M. Krengli MD PhD[15], A. Gomez-Brouchet MD PhD[16], P. Sargos MD PhD[1], G. Rochcongar MD [17], C. Bazille MD[18], V. Roth MD MSc[19], J. Salleron MSc[14] and J. Thariat MD PhD [4,20,21]

[1]Department of Radiation Oncology. Institut Bergonie, Bordeaux, France, [2]Institut Gustave Roussy, Villejuif, France, [3]Assistance Publique Hôpitaux de Marseille, Timone Hospital, Marseille, France, [4]Department of Radiation Oncology. Centre Baclesse / ARCHADE – Normandie Université, Caen, France, [5]Centre Léon Berard, Lyon, France, [6]Institut de Cancérologie de Lorraine, Vandoeuvre Les Nancy, France, [7]Clinica Instituto de Radiomedicina (IRAM), Santiago, Chile, [8]Radiation Oncology, Geneva University Hospital, Geneva, Switzerland, [9]Rambam HCC, Haïfa, Israël, [10]Centre Hospitalier Universitaire Vaudois (CHUV), Department of Radiation Oncology, Lausanne, Switzerland, [11]Hospital General Universitario Gregorio Marañón, Madrid, Spain, [12]IUCT-Oncopole, Toulouse, France, [13]Centre Hospitalier Régional Universitaire "Jean Minjoz", Université de Bourgogne - Franche Comté, Besançon, INSERM UMR 1098 France, [14]Department of Biostatistics, Institut de Cancérologie de Lorraine, Université de Lorraine, F-54500 Vandœuvre-lès-Nancy, France, [15] Department of Radiation Oncology, University Hospital, Novara, Italy; [16] Department of Pathology, University Hospital of Toulouse, Toulouse, France, [17] Department of orthopedics, University Hospital of Caen, France, [18] Department of pathology, University Hospital of Caen, France, [19] Easy-CRF SAS, [20] Laboratoire de physique corpusculaire IN2P3/ENSICAEN - UMR6534, [21] Unicaen - Normandie Université

Corresponding author:

Juliette Thariat
Department of Radiation Oncology, Centre Baclesse / ARCHADE – Normandie Université –, 4 rue General Harris. Caen, France
Tel: 33231455050; Fax: 33231455000; Email : jthariat@gmail.com

Responsible authors for statistical analyses: Juliette Thariat (cf. address) and Julia Salleron

Julia Salleron
Department of Biostatistics, Institut de Cancérologie de Lorraine, Université de Lorraine, F-54500 Vandœuvre-lès-Nancy, France 6 avenue de Bourgogne - CS 30519 54519 Vandœuvre-lès-Nancy Cedex
Tel : 33383598664 ; Email : j.salleron@nancy.unicancer.fr

Conflict of interest: none

Funding : none

Presentation: SFRO and ASTRO 2018 Poster #: MO_41_2862 Title: Radiotherapy in Extracranial Chondrosarcomas: A multicenter French Sarcoma Group and Rare Cancer Network study

Original article

Postoperative radiotherapy in patients with extracranial chondrosarcoma, a joint study of the French Sarcoma Group and Rare Cancer Network

Running head: **Radiotherapy in extracranial chondrosarcoma**

Abstract:

Background: Postoperative radiotherapy (poRT) of intracranial/skull base chondrosarcomas is standard treatment. However, consensus is lacking for poRT in extracranial CHS (eCHS) due to easier resectability and intrinsic radioresistance. We assessed practice and efficacy of poRT in extracranial CHS. **Patients and methods**: This multicentric retrospective study of the French Sarcoma Group / Rare Cancer Network included patients with eCHS operated on between 1985 and 2015. Inverse propensity score weighting (IPTW) was used to minimize poRT allocation biases. **Results:** Of 182 patients, 60.4% had bone and 39.6% soft-tissue eCHS. eCHS were of conventional (31.9%), myxoid (28.6%, 41 extraskeletal (EMC), 11 skeletal), mesenchymal (9.9%), or other subtypes. En-bloc surgery with complete resection was performed in 52.6% and poRT in 36.8% of patients (median dose 54 Gy). Irradiated patients had unfavorable initial characteristics, with higher grade and incomplete resection. Median follow-up time was 61 months. Five-year incidence of local relapse was 10% with poRT *vs* 21.6% without (p=0.050). Using IPTW method, poRT reduced the local relapse risk (HR 0.27, 95% CI [0.14; 0.52], p<0.001). Five-year disease-free survival (DFS) was 71.8% with poRT and 64.2% without (p=0.680). Using IPTW method, poRT improved DFS (HR 0.51 [0.30;0.85], p=0.010). The benefit of poRT on local relapse and DFS was confirmed after exclusion of EMC. There was no difference in overall survival. Prognostic factors of poorer DFS in multivariate analysis were deeper location, higher grade, incomplete resection and no

poRT. **Conclusion**: poRT should be offered in eCHS patients with high grade or incomplete resection, regardless of histological subtype.

Key words: chondrosarcoma, radiotherapy, surgery, postoperative / adjuvant, myxoid, mesenchymal, bone, soft tissue, radioresistance, survival

Introduction

Chondrosarcomas (CHS) are a rare sarcoma subtype of bone and soft tissues [1]. They are characterized by their chemo- and radioresistance [2], attributed to their tissue phenotype with slow proliferation rate, poor vascularization and dense cartilaginous matrix limiting oxygen accessibility to cells [3]. Surgery with wide margins remains the standard of care. Age at diagnosis, histological grade, size and tumor site are consistent prognostic factors [4]. In skull base CHS, en-bloc resection with negative margins is rarely achievable and surgery can be associated with major sequelae of the cranial nerves. In these cases, described by some as “high-risk of relapse” situations [5], definitive radiotherapy (RT) or postoperative radiotherapy (poRT) is frequently required. Achieving a high-dose, in the order of 70 Gy, can be challenging if radiosensitive dose-limiting organs at risk or tissues are close to the tumor. However, skull base CHS have become a consolidated indication of RT with protons due to their better spatial distribution than photons used in conventional RT [6, 7]. The combination of proton therapy and surgery has consistently shown better local control rates and lower morbidity using marginal resection and dose-escalated proton therapy [8]. Other anatomic sites than the skull base are hardly treated with poRT owing to the old radioresistance concept although RT has evolved in such a way that high dose (≥ 60 Gy) can be delivered with limited clinically significant damage in normal tissues. There is no clear consensus regarding the place of poRT in extracranial CHS (eCHS). Decision for poRT is usually made during multidisciplinary sarcoma meetings regardless of CHS subtype, due to lack of specific data on tumor response to RT by CHS subtype. The main objective of our study was to assess current practice and efficacy of poRT in eCHS.

Material and methods

This retrospective multicentric institutional review-board (IRB) and ethics committee approved (Groupe Sarcome Français GSF-GETO and Rare Cancer Network RCN) study included all eCHS treated between 1985 and 2015. Data were collected on the secured encrypted website www.easy-crf.com. Base of skull and other intracranial CHS, palliative cases or unresectable / inoperable tumors were excluded. Treatments were discussed on a multidisciplinary sarcoma board. All surgical and RT treatment techniques were allowed. Tumors were centrally reviewed by expert pathologists (RREPS et RESOS) and all histological CHS subtypes were included. Analyses were first conducted considering all histologic subtypes and secondly after extraskeletal myxoid chondrosarcoma (EMC) exclusion, knowing their recent reclassification [23].

Statistics

Quantitative parameters were described by median and interquartile range, qualitative parameters by frequency and percentage. Normality of quantitative parameters was investigated by the Shapiro-Wilk test. Incidence of local relapse was described with the Fine and Gray model, to take into account competing risks such as emergence of metastases or death whatever the cause [9]. The Kaplan–Meier method was performed to describe overall survival (OS) and disease free survival (DFS) defined as the time lapse between the date of diagnosis and the date of relapse or death, whatever the cause [9]. Local relapse incidence was compared according to poRT using the bivariate Fine-Gray model. Due to potential selection biases (i.e. the choice of poRT could be done according to patient and tumor characteristics), the results of these bivariate analyses had to be adjusted based on major

prognostic factors. The inverse probability of treatment weighting (IPTW) method was applied for the adjustment [10]. The propensity score was computed with either the presence or absence of poRT as dependent parameters, and with all described patient and tumor characteristics and the inverse probability of treatment – poRT- was computed. Comparisons of patient and tumor characteristics were performed after weighting on a propensity score in order to check whether imbalances between surgery alone or surgery and poRT were eliminated. The effects of poRT on local relapse, DFS and OS were estimated by the hazard ratios after adjusting on this propensity score (i.e. using the IPTW method). A sensitivity analysis excluding patients with EMC was then conducted by applying the previously described process.

The prognostic value of each factor on local relapse was then studied using the bivariate Fine-Gray model, and the results were expressed with the sub-distribution hazard ratio (SHR) and its 95% confidence intervals. Parameters with a p-value less than 0.1 in bivariate analysis were selected for the multivariate Fine-Gray model. A simplification of this full model was done with a bootstrap-model selection procedure [11], and backward selection. The same process was performed to investigate prognostic factors of DFS and OS by using the Cox proportional-hazards model and results were expressed with their hazard ratio (HR) and 95% confidence intervals. Exploratory subgroup analyses on DFS were performed to identify subgroups of patients who would have the greatest benefit from poRT by investigating the interaction between poRT and major prognostic factors. Results were illustrated by a forest plot. All statistical analyses were performed using SAS software, v9.4 (SAS Institute Inc., Cary, NC 25513). P-values <0.05 were considered statistically significant.

Results

One hundred and eighty-two patients with eCHS were included. The description of the population selection process is shown in supplementary figure 1 (online). There were 110 bone CHS (60.4%) and 72 soft tissue CHS (39.6%). Of 32 thoracic bone CHS, 17 cases were located in the ribs. eCHS included several subtype cases: 58 conventional (31.9%), 52 myxoid (28.6%), 18 mesenchymal (9.9%), 9 dedifferentiated (4.9%), 7 periosteal (3.8%), 3 clear cell (1.6%), 11 of various other rare subtypes (6%) and 24 not otherwise specified. Among myxoid CHS 41 originated from soft tissues (EMC) and 11 in bone/cartilage.

All patients had undergone surgery, including complete resection in 101 (55.5%) patients. En-bloc surgery with complete resection (R0) was observed in 51/103 (49.5%) patients with bone CHS and 39/68 (57.3%) patients with soft tissue CHS (p=0.541; margin status missing in 11).

Sixty-seven patients (36.8%) received poRT, which consisted of 3D-conformal poRT in 44 (65.7%), intensity modulated radiotherapy (IMRT) in 19 (28.4%) or proton therapy in 4 (5.9%) patients. Median dose was 54.0 Gy, interquartile range IQR (50.0-62.8). Dose was different depending on R0 (N=29 patients), with a median dose 50.4 Gy (IQR 50.0-59.4), R1 (N=24 patients), 59.7 Gy (IQR 50.0-63.0) or R2 (N=9 patients), 70 Gy (IQR 64-70) status (p=0.002). Mean patient number per center was 11 (median 9; range 1-31). poRT was variably performed among centers: for those (N=6) including ≥10 patients, rates of poRT varied between 3.7% and 67%, p<0.001. Chemotherapy was delivered in 4.8% (4/84), 12.3% (9/73) and 32.0% (18/25) of patients with grade 1, 2 or 3 eCHS patients (p<0.001).

Proportions of grade 3 CHS, en-bloc and R0 resection varied between centers. Patient and tumor characteristics were different between poRT or surgery alone patients (Table 1).

Patients who underwent poRT had larger, deeper and higher-grade tumors and more likely had soft tissue or incompletely resected (R1/R2) CHS (Table 1). Comparison of patient and tumor characteristics by poRT using the IPTW method is presented in Table 2: Tumor size was missing in 31 patients. Tumor size was consequently not used for propensity score analyses and was not well balanced between the two groups.

Impact of poRT on outcomes

Median follow-up was 61 months (IQR 24-107). The third quartile of living patients had 120-months of follow-up. The number of events for each outcome is summarized in Supplementary table 1. There were 29 local relapses. Median time to local relapse was 15.9 months (IQR 7.1-32.2). The 5-year incidence of local relapse was 16.9% (95% confidence interval, 95%CI: 11.4 - 23.3), with 10% (95%CI [4.0; 19.2]) in patients with poRT versus 21.6% (95%CI [13.6; 37]) in patients without poRT. The 10-year incidence of local relapse was 12.5% (95%CI [5.3; 22.9]) with poRT and 26.7% (95%CI [16.7; 37.8]) without poRT (SHR 0.43, 95%CI [0.19;1.00], p=0.050, Figure 1a). After IPTW method to adjust on selection bias, poRT significantly reduced the risk of local relapse (SHR 0.27, 95%CI [0.14; 0.52], p<0.001). This improvement in local control rate was confirmed when EMC were excluded from analysis (N=130) with a lower incidence of local relapse for patients undergoing poRT (SHR 0.21, 95%CI [0.10-0.42], p<0.001).

At last follow up, 29 patients had had a local relapse, 5 had had a regional (nodal) relapse, 29 had had a metastatic relapse, 2 had died of disease and one had died of another cause. All the nodal relapses occurred in non-irradiated patients. The 5-year disease-free survival (DFS) rate was 67.2% (95%CI [59.0;74.1]), with 64.2% (95%CI [53.2; 73.2]) in patients without poRT versus 71.8% (95%CI [58.5; 81.5]) in patients with poRT. At 10 years, DFS rate was 48.0%

(95%CI [37.6;57.7]) overall, 55.6% (95%CI [39.3;69.1]) with poRT and 41.1% (95%CI [27.2; 54.5]) without. There was not significant difference according to poRT (HR 0.67, 95%CI [0.41;1.12], p=0.680, Figure 1b). After IPTW method to adjust on selection bias, poRT significantly improved the DFS (HR 0.51, 95%CI [0.30; 0.85], p=0.010). This improvement in DFS was confirmed after the exclusion of EMC (HR 0.51[0.28-0.93], p<0.001).

The 5-year overall survival (OS) was 80.0% (95%CI [72.3;85.7]). At five years, OS was 77.8% (95%CI [64.8;86.5]) with poRT versus 80.0% (95%CI [69.5;87.2]) without (HR 1.03, 95%CI [0.55;1.94], p= 0.927, Figure 1c). OS was similar with or without poRT using IPTW method (HR 0.79, 95% CI [0.43 ;1.45], p= 0.445) and after the exclusion of EMC (HR 0.72[0.38-1.37], p=0.322). For each outcome, results and those using the IPTW method are summarized in Supplementary table 2.

Prognostic factors

In bivariate analysis, piecemeal or incomplete resection and absence of RT were significantly associated with higher incidence of local relapse (Table 3). The incidence of local relapse at 60 months was 5.0% [1.6%;11.4%] for patients with en-bloc resection and R0 margins, 18.8% [9.2%;31.2%] for patients with en-bloc resection and R1/R2 margins or patients with piecemeal resection and R0 margins. The incidence of local relapse at 60 months was 47.1% [22.2%;68.6%] for patients with piecemeal resection and R1/R2 margins (p<0.001). Quality of resection (R0 *vs* R1/R2) combined with en-bloc resection, EMC and poRT were associated with lower local relapse rates on multivariate analysis (Table 3).

In bivariate analysis, larger tumor size, deeper location, higher grade (grade 2-3), piecemeal or incomplete resection were associated with poorer DFS whereas the head and neck location was associated with better DFS (Table 4). In multivariate analysis, four parameters

remained significantly associated with a poorer DFS: deeper location, higher grade (grade 2-3), incomplete resection and absence of poRT (Table 4).

In bivariate analysis, larger tumor size, deeper location, grade 2-3 and chemotherapy were associated with poorer OS. In multivariate analysis, deeper location and grade 2-3 were associated with poorer OS whereas EMC was associated with a better OS (Table 4).

Selection criteria for poRT

No difference in poRT efficacy was found with the following prognostic factors: tissue of origin (bone or soft tissues), tumor depth, tumor size >5 *vs* ≤5 cm, en-bloc resection or not (interaction test not significant). In contrast, poRT was even more beneficial on DFS in grade 2/3 compared to grade 1 CHS and in incompletely resected CHS (Figure 2).

Discussion

Based on the observation of a benefit of poRT in local relapse-free survival, DFS and OS for intracranial/skull base CHS across studies [12], we addressed the controversial role of poRT in the curative approach of eCHS. Quality of surgery is of utmost importance in sarcomas, but it can be challenging in CHS, especially in terms of functional outcomes so that intralesional resection in low-grade CHS is an option [13]. Data on poRT in eCHS and data on molecular signatures of radiation response are lacking. Thus, the decision for poRT in eCHS is currently made during multidisciplinary staff meetings with no attempt to predict radiation response based on histological subtype or their intrinsic molecular characteristics. We thus performed an analysis of the benefit of poRT in eCHS and also analyzed the influence of histological subtype, with a focus on extraskeletal myxoid CHS (EMC).

Firstly, this cooperative multicentric retrospective study showed that poRT significantly improved local control rates. Five- and ten-year local relapse rates decreased with poRT from 21.6% to 10% and from 26.7% to 12.5%, respectively. These results are consistent with a previous series by Goda *et al.* where a 90% 10-year local control rate was observed for high-risk eCHS treated by surgery with preoperative RT or poRT. Patients and tumors characteristics were similar between their series and ours [5]. More interestingly, piecemeal or incomplete resection were observed in our series in almost half of the patients but less than half of them underwent poRT, which shows the lack of a clear consensus on its indication. We observed that patients undergoing poRT had unfavorable tumor characteristics and incomplete resection overall but practices with respect to referral for poRT among centers were indeed heterogeneous. Median poRT dose was 54 Gy, with dose adaptation on the quality of resection: median dose was 50.4, 60 and 70 Gy in patients with R0, R1 and R2 disease respectively. These doses were lower than those recommended by NCCN [14], which may suggest the possibility of greater benefit of poRT using higher doses. Considering that eCHS located in complex tumor anatomies such as paraspinal and pelvic locations are sometimes treated with IMRT or proton therapy [15-20], radioresistance of CHS may appear as only a relative contraindication for poRT. Thus, poRT is worth being investigated further [21].

Secondly, we observed that poRT improved five-year DFS rates from 64.2% to 71.8% but had no impact on OS. Adjusting for selection biases using IPTW, this benefit was even larger: poRT improved DFS by 75% (HR 0.25), which was confirmed by bootstrap resampling [11]. Interaction test carried out established which profile of CHS benefits the most from poRT (Figure 2). High-grade subtypes (grade 2-3) and incomplete resection appeared as decision criteria for poRT. High-grade is a classical prognostic factor in the literature [22] and it was

associated with a benefit on local control and DFS (which included metastases as an event) from poRT in the current series. However, we found that poRT did not improve OS, possibly reflecting that metastatic failures were responsible for deaths. It is indeed frequent in sarcoma studies that there is no impact of local control on survival. It is also possible that unmeasured confounders (i.e. residual biases) had an effect even after IPTW adjustment. The sole residual unbalanced factor propensity score computation (not computed due to missing data) was tumor size. Despite larger tumor size in the poRT group, poRT had a benefit on local control and DFS after IPTW.

Interestingly, exclusion of EMC, an entity that is now considered different from CHS due to distinct molecular characteristics, did not change the observed benefits in the poRT group. It might be needed to assess radiation response correlate with molecular characteristics before changing a decision for RT.

In our study, we first considered CHS together regardless of histological subtypes. This was guided by our clinical practice, where the decision to prescribe poRT does not currently depend so much on histological subtype as on tumor grade or surgical considerations. Hence, our series included several histologies, including EMC. This should be considered as a means to accurately decipher different radiosensitivity behaviors among CHS subtypes. Especially EMC were recently classified as a subtype of soft tissue tumors with uncertain differentiation according to the World Health Organization Classification of Tumors of Soft Tissue and Bone [23] and to some, should not be considered as CHS. Of 52 (28.6%) myxoid CHS, 41 EMC were however included as CHS by centers belonging to the GSF-GETO, with histology being centrally-reviewed by expert pathologists. This histological subtype is characterized by the translocation t(9;22)(q22;q12), resulting from the fusion of *EWSR1* and *NRA3* [24] or a translocation between *NRA3* and *TAF15* or *TCF12* [24-26].

However, such analyses are not done yet in routine practice. A more thorough molecular characterization would be important if a drug-targetable gene is identified but it is uncertain whether molecular characterization influences radiation response. Moreover, because there are no therapeutic recommendations specific to EMC, most radiation oncologists thus consider EMC as one CHS subtype. From the RT point-of-view, the cellular and tissue characteristics such as matrix abundance and hypoxia of cancer cells are more likely to influence radiation response. In a previous series of 156 patients with EMC of whom 50 (32%) underwent poRT , Kemmerer *et al.* observed a 9% absolute benefit in IPTW-confirmed cancer-specific survival with the addition of poRT (p=0.02) with a trend toward survival benefit [27]. In our studies, interaction tests suggested a greater benefit on DFS for EMC than other subtypes. To avoid possible selection biases and to take into account the current CHS classification, we conducted additional subgroups analyzes, distinguishing EMC and others. When our series was analyzed after EMC exclusion (N=141) and with weighting by the inverse propensity score, improvement in local control rates and DFS were confirmed.

Finally, poRT was efficient in bone and soft tissue CHS overall (Tables 3-4) but there appeared to be a larger benefit for soft tissue ones (Figure 2). The benefit in our series was marginal in bone CHS but was significant in other series [28]. Soft tissue CHS seem more aggressive and prone to respond to radiotherapy in our series and others [29,30]. It is important to note that piecemeal surgery of bone CHS is frequently performed by curettage in low-grade CHS [31], with variations between tumor sites and functional impact [32].

Another important observation was that there were as many patients with a local relapse as those with a metastatic failure. Moreover, adjuvant chemotherapy was administered in high-grade CHS and was consequently associated with a higher risk of death in this series in

bivariate analysis (Table 4). Despite such observation, poRT remained beneficial on DFS for the entire cohort.

Our study has some limitations. Firstly, its retrospective design could limit its broad applicability but the rarity of eCHS prevents efficient prospective assessment of poRT benefit. Secondly, our study included data collected on a long time span. Although potential changes in modalities of surgery, RT practice and systematic molecular analyses (impact of which remains to be demonstrated on radiation response) may have taken place, if a shorter time interval had been decided to limit the heterogeneity of these parameters, the sample size would probably not have been sufficient to conduct such an analysis. For these reasons, other large series have also been performed on periods of 30 years or so. Noteworthy, RT techniques have improved during that period. The majority of irradiated patients in our series were treated with 3D modalities (65.7%). The development of IMRT has enabled better dose distributions, potentially allowing dose escalation and it is likely that the benefit of poRT would be better due to a greater risk-benefit ratio [33][34].

In conclusion, this large series of 182 patients with eCHS shows a benefit of poRT in terms of local control rate and DFS regardless of histological subtype, which was confirmed after exclusion of EMC. Although the observed benefit was greater for EMC, confirming their radiosensitivity, our results call into question the assumed radioresistance of the other CHS. In addition to highlighting the importance of surgical resection, our series shows that poRT should be indicated for selected cases such as high grade or incompletely resected CHS. Thus, it may be considered that selected cases of eCHS should be offered poRT, using optimal poRT techniques that may be photon-based therapies or hadrontherapy.

References

1. Dorfman HD, Czerniak B. Bone cancers. Cancer 1995; 75: 203-210.

2. Moussavi-Harami F, Mollano A, Martin JA et al. Intrinsic radiation resistance in human chondrosarcoma cells. Biochem Biophys Res Commun 2006; 346: 379-385.

3. Eke I, Cordes N. Radiobiology goes 3D: how ECM and cell morphology impact on cell survival after irradiation. Radiother Oncol 2011; 99: 271-278.

4. van Praag Veroniek VM, Rueten-Budde AJ, Ho V et al. Incidence, outcomes and prognostic factors during 25 years of treatment of chondrosarcomas. Surg Oncol 2018; 27: 402-408.

5. Goda JS, Ferguson PC, O'Sullivan B et al. High-risk extracranial chondrosarcoma: long-term results of surgery and radiation therapy. Cancer 2011; 117: 2513-2519.

6. Weber DC, Murray F, Combescure C et al. Long term outcome of skull-base chondrosarcoma patients treated with high-dose proton therapy with or without conventional radiation therapy. Radiother Oncol 2018; 129: 520-526.

7. Mattke M, Vogt K, Bougatf N et al. High control rates of proton- and carbon-ion-beam treatment with intensity-modulated active raster scanning in 101 patients with skull base chondrosarcoma at the Heidelberg Ion Beam Therapy Center. Cancer 2018; 124: 2036-2044.

8. Simon F, Feuvret L, Bresson D et al. Surgery and protontherapy in Grade I and II skull base chondrosarcoma: A comparative retrospective study. PLoS One 2018; 13: e0208786.

9. Bellera CA, Penel N, Ouali M et al. Guidelines for time-to-event end point definitions in sarcomas and gastrointestinal stromal tumors (GIST) trials: results of the DATECAN initiative (Definition for the Assessment of Time-to-event Endpoints in CANcer trials)dagger. Ann Oncol 2015; 26: 865-872.

10. Rosenbaum PR. Optimal Matching for Observational Studies. Journal of the American Statistical Association 1989; 84: 1024-1032.

11. Sauerbrei W, Schumacher M. A bootstrap resampling procedure for model building: application to the Cox regression model. Stat Med 1992; 11:2093-2109 1992; 11: 2093-20109.

12. Mercado CE, Holtzman AL, Rotondo R et al. Proton therapy for skull base tumors: A review of clinical outcomes for chordomas and chondrosarcomas. Head Neck 2019; 41: 536-541.

13. Chen X, Yu LJ, Peng HM et al. Is intralesional resection suitable for central grade 1 chondrosarcoma: A systematic review and updated meta-analysis. Eur J Surg Oncol 2017; 43: 1718-1726.

14. Biermann JS, Chow W, Reed DR et al. NCCN Guidelines Insights: Bone Cancer, Version 2.2017. J Natl Compr Canc Netw 2017; 15(2): 155-167

15. De Amorim Bernstein K, DeLaney T. Chordomas and chondrosarcomas-The role of radiation therapy. J Surg Oncol 2016; 114: 564-569.

16. De Amorim Bernstein K, Liebsch N, Chen YL et al. Clinical outcomes for patients after surgery and radiation therapy for mesenchymal chondrosarcomas. J Surg Oncol 2016; 114: 982-986.

17. DeLaney TF, Liebsch NJ, Pedlow FX et al. Long-term results of Phase II study of high dose photon/proton radiotherapy in the management of spine chordomas, chondrosarcomas, and other sarcomas. J Surg Oncol 2014; 110: 115-122.

18. Demizu Y, Jin D, Sulaiman NS et al. Particle Therapy Using Protons or Carbon Ions for Unresectable or Incompletely Resected Bone and Soft Tissue Sarcomas of the Pelvis. Int J Radiat Oncol Biol Phys 2017; 98: 367-374.

19. Demizu Y, Mizumoto M, Onoe T et al. Proton beam therapy for bone sarcomas of the skull base and spine: A retrospective nationwide multicenter study in Japan. Cancer Sci 2017; 108: 972-977.

20. Indelicato DJ, Rotondo RL, Begosh-Mayne D et al. A Prospective Outcomes Study of Proton Therapy for Chordomas and Chondrosarcomas of the Spine. Int J Radiat Oncol Biol Phys 2016; 95: 297-303.

21. Hamdi DH, Barbieri S, Chevalier F et al. In vitro engineering of human 3D chondrosarcoma: a preclinical model relevant for investigations of radiation quality impact. BMC Cancer 2015; 15: 579.

22. Evans HL, Ayala AG, Romsdahl MM. Prognostic factors in chondrosarcoma of bone: a clinicopathologic analysis with emphasis on histologic grading. Cancer 1977; 40: 818-831.

23. Lucas DR, G. Stenman, Fletcher CD et al. Pathology and Genetics of Tumours of Soft Tissue and Bone. Lyon, France: International Agency for Research on Cancer,2013.

24. Chow WA. Chondrosarcoma: biology, genetics, and epigenetics. F1000Res 2018; 7.

25. Kilpatrick SE, Inwards CY, Fletcher CD et al. Myxoid chondrosarcoma (chordoid sarcoma) of bone: a report of two cases and review of the literature. Cancer 1997; 79: 1903-1910.

26. Zhang L, Wang R, Xu R et al. Extraskeletal Myxoid Chondrosarcoma: A Comparative Study of Imaging and Pathology. Biomed Res Int 2018; 2018: 9684268.

27. Kemmerer EJ, Gleeson E, Poli J et al. Benefit of Radiotherapy in Extraskeletal Myxoid Chondrosarcoma: A Propensity Score Weighted Population-based Analysis of the SEER Database. Am J Clin Oncol 2018; 41: 674-680.

28. Shives TC, McLeod RA, Unni KK, Schray MF. Chondrosarcoma of the spine. J Bone Joint Surg Am 1989; 71: 1158-1165.

29. Thorkildsen J, Taksdal I, Bjerkehagen B et al. Chondrosarcoma in Norway 1990-2013; an epidemiological and prognostic observational study of a complete national cohort. Acta Oncol 2019; 1-10.

30. Nota SP, Braun Y, Schwab JH et al. The Identification of Prognostic Factors and Survival Statistics of Conventional Central Chondrosarcoma. Sarcoma 2015; 2015: 623746.

31. Gerbers JG, Dierselhuis EF, Stevens M et al. Computer-assisted surgery compared to fluoroscopy in curettage of atypical cartilaginous tumors / chondrosarcoma grade 1 in the long bones. PLoS One 2018; 13: e0197033.

32. Rizzo M, Ghert MA, Harrelson JM, Scully SP. Chondrosarcoma of bone: analysis of 108 cases and evaluation for predictors of outcome. Clin Orthop Relat Res 2001; 224-233.

33. Chan MF, Chui CS, Schupak K et al. The treatment of large extraskeletal chondrosarcoma of the leg: comparison of IMRT and conformal radiotherapy techniques. J Appl Clin Med Phys 2001; 2: 3-8.

34. Catanzano AA, Kerr DL, Lazarides AL, et al. Revisiting the Role of Radiation Therapy in Chondrosarcoma: A National Cancer Database Study. Sarcoma. 2019;2019:4878512. Published 2019 Oct 13.

FIGURE CAPTIONS

Figure 1: a local relapse by poRT, ***b*** DFS by poRT, ***c*** OS by poRT with statistical significance before (p-value) and after IPTW method ($p\text{-value}_{IPTW}$).

Legend: poRT postoperative radiotherapy

Figure 2: Forest plot of selection criteria for poRT (based on DFS)

Legend: poRT postoperative radiotherapy

TABLES

Table 1 Patient and tumor characteristics by postoperative radiotherapy (poRT)

Table 2 Description and comparison of patient and tumor characteristics by postoperative radiotherapy after using inverse probability treatment weighting (IPTW method)

Table 3 Prognostic factors of local relapse in bivariate and multivariate models based on Fine and Gray sub-distribution hazard function

Table 4 Prognostic factors of disease-free survival and overall survival by bivariate and multivariate Cox proportional hazard models

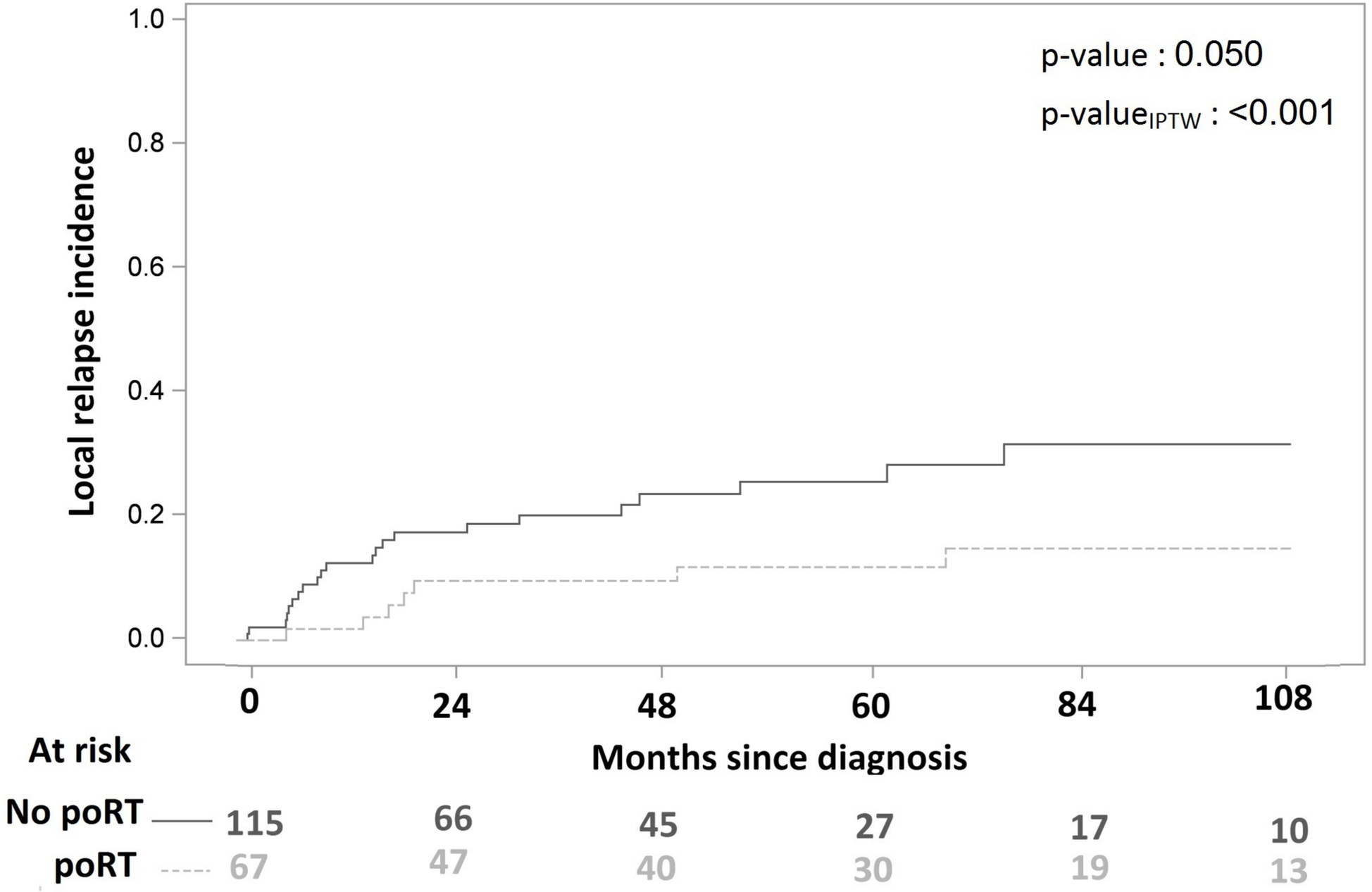

Figure 1a: Local relapse

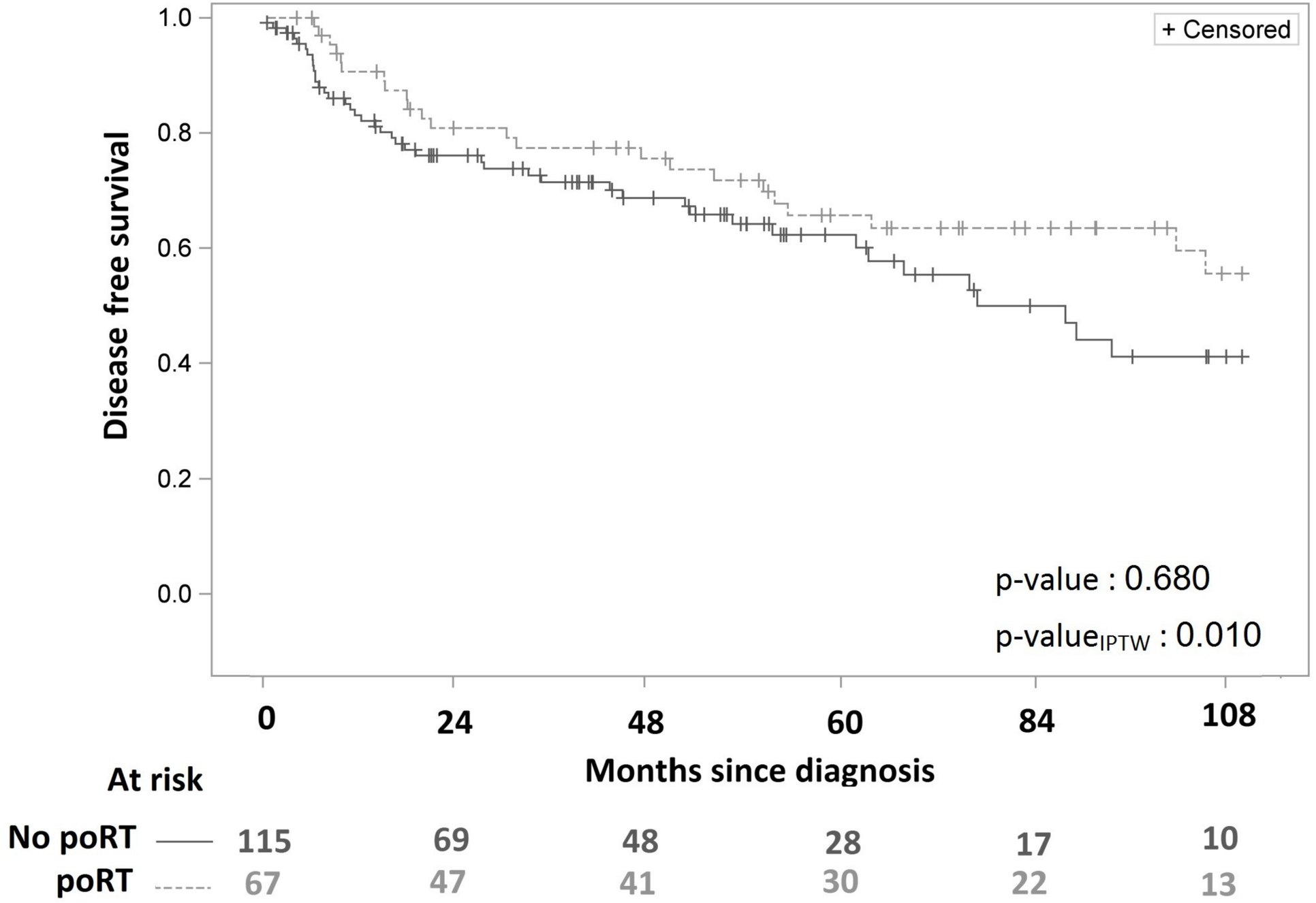

Figure 1b: Disease-free survival

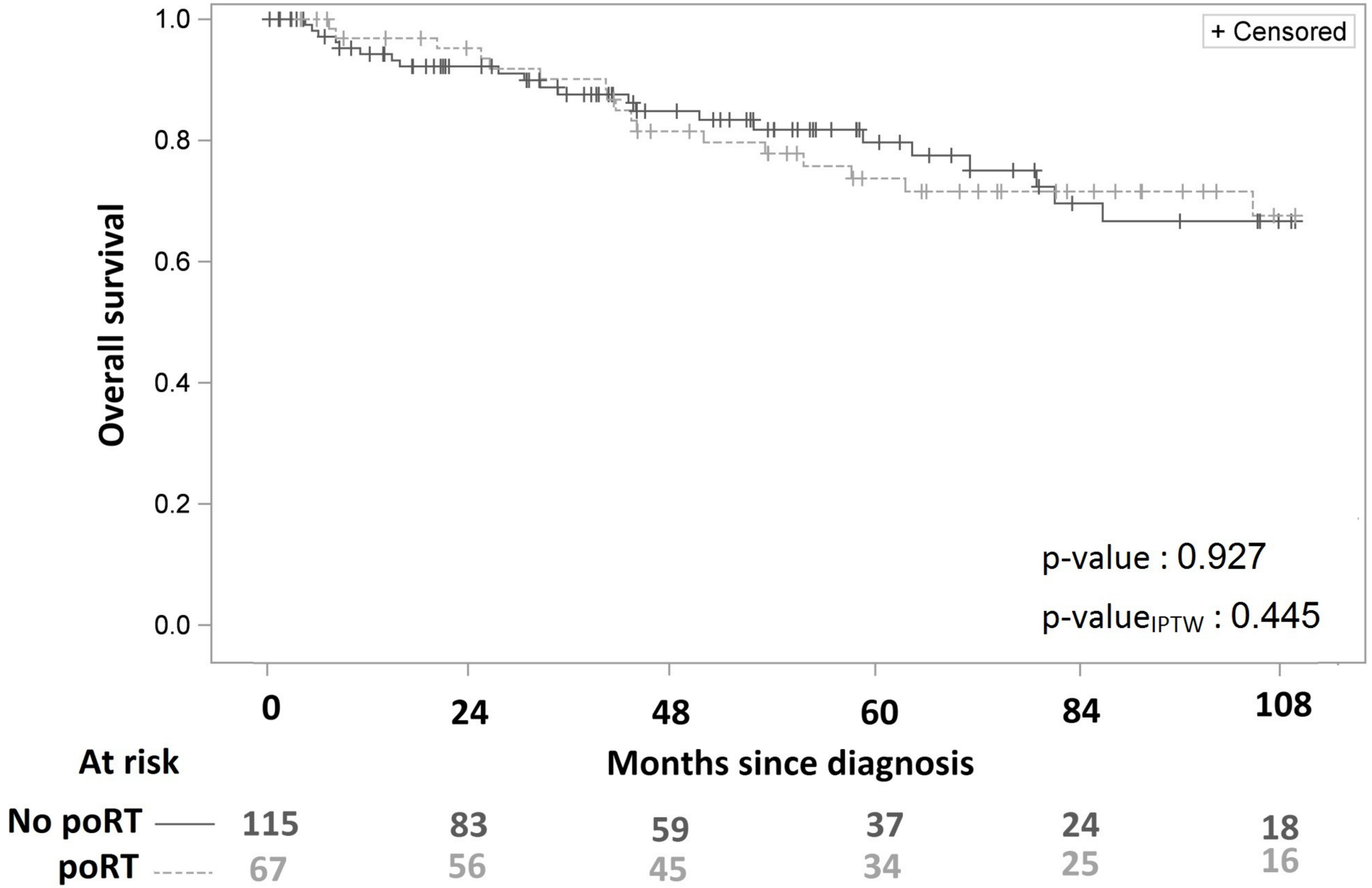

Figure 1c: Overall survival

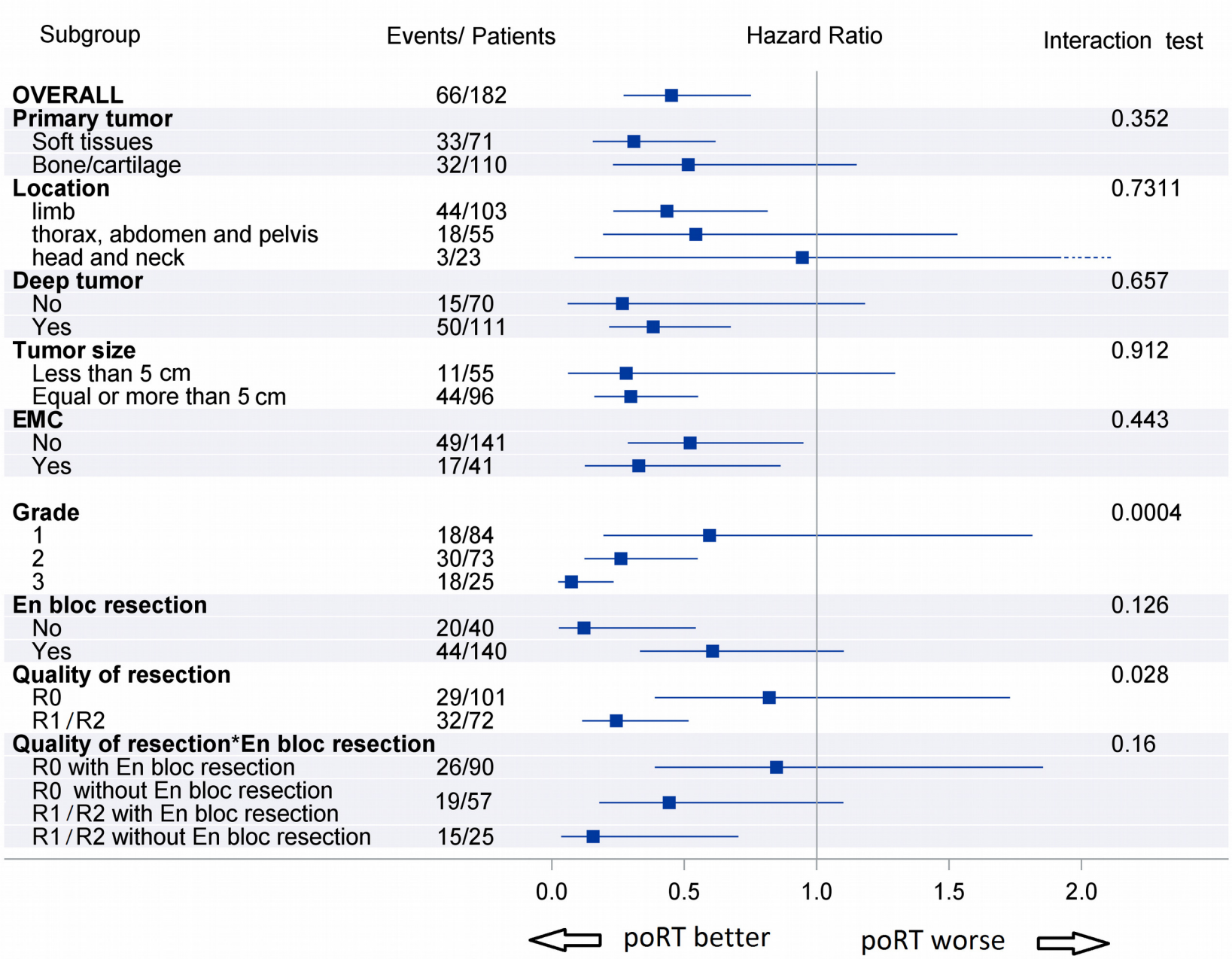

Figure 2: Forest plot of selection criteria for poRT (based on DFS)

Legend: poRT postoperative radiotherapy

Table 1 Patient and tumor characteristics by postoperative radiotherapy (poRT)

	Without radiotherapy (n = 115)	With postoperative radiotherapy (n = 67)	*P*
Sex			.273
Male	59 (51.3%)	40 (59.7%)	
Female	56 (48.7%)	27 (40.3%)	
Mean age (yo)	51 [37 - 64]	50 [35 - 63]	.526
Age (yo)			.765
<50	54 (47.0%)	33 (49.25%)	
≥50	61 (53.0%)	34 (50.75%)	
Primary tumor tissue of origin			.001
Bone	80(69.8%)	30(43.3%)	
Soft tissues	35(30.1%)	37(55.2%)	
Location			.026
Limb	68 (60.8%)	32 (52.4%)	
Thorax, abdomen and pelvis	37 (33.0%)	17 (27.9%)	
Head and neck	7 (6.2%)	12 (19.7%)	
Mean tumor size (cm)	5.5 [3.0 – 10.0]	7.0 [4.0 – 10.0]	.153
Tumor size‡			.055
<5	38(42.7%)	17(27.4%)	
≥5	51(57.3%)	45(72.6%)	
Deep tumor	61 (53.0%)	50 (75.8%)	.003
Grade			<.001
1	67 (58.2%)	17 (25.4%)	
2	37 (32.2%)	36 (53.7%)	
3	11 (9.6%)	14 (20.9%)	
EMC	20 (17.4%)	21 (31.3%)	.029
En bloc resection (EBR)	84 (73.0%)	56 (83.6%)	.206
Quality of resection			.030
R0	71 (64.55%)	30 (47.6%)	
R1/R2	39 (35.45%)	34(52.4%)	
Resection			.055
R0 with EBR	62(56.9%)	28(44.4%)	
R0 without EBR or R1/2 with EBR	29(26.6%)	28(44.4%)	
R1/2 without EBR	18(16.5%)	7(11.1%)	
Chemotherapy	9 (7.8%)	12 (17.9%)	.040
Timing of chemotherapy*			.674
Neo-adjuvant	4 (44.4%)	5 (41.7%)	
Adjuvant	5 (55.6%)	6 (50.0%)	
Concomitant	0 (0%)	1 (8.3%)	

Abbreviations: yo = years old; EMC = Extraskeletal Myxoid Chondrosarcoma; EBR = En bloc resection

*Among patients with chemotherapy

‡ 31 missing data

Table 2 Description and comparison of patient and tumor characteristics by postoperative radiotherapy after using inverse probability treatment weighting (IPTW method)

	Without radiotherapy (n = 115)	With postoperative radiotherapy (n = 67)	*P*
Sex			.338
Male	55.2%	60.5%	
Female	44.8%	39.5%	
Mean age (yo)	50.1±20.4	49.8±25.7	.913
Age (yo)			.868
<50	48.6%	49.6%	
≥50	51.4%	50.4%	
Primary tumor tissue of origin			.304
Bone	55.9%	50.1%	
Soft tissues	44.1%	49.9%	
Location			.536
Limb	61.5%	58.5%	
Thorax, abdomen and pelvis	30.0%	29.2%	
Head and neck	8.5%	12.3%	
Mean tumor size (cm)‡	7.6±7.4	9.3±14.9	.225
Tumor size (cm)‡			.010
<5	38.2%	23.9%	
≥5	61.8%	76.1%	
Deep tumor	65.3%	75.2%	.055
Grade			.178
1	46.1%	36.1%	
2	39.7%	48.7%	
3	14.2%	15.2%	
EMC	24.3%	28.4%	.400
En bloc resection (EBR)	80.3%	81.6%	.768
Quality of resection			.312
R0	57.0%	51.3%	
R1/R2	43.0%	48.7%	
Resection			.720
R0 with EBR	51.5%	50.5%	
R0 without EBR or R1/2 with EBR	34.2%	32.0%	
R1/2 without EBR	14.3%	17.5%	
Chemotherapy	12.5%	14.5%	.609
Timing of chemotherapy*			.514
Neo-adjuvant	34.0%	34.2%	
Adjuvant	66.0%	60.0%	
Concomitant	0	5.8%	

Abbreviations: yo = years old; EMC = Extraskeletal Myxoid Chondrosarcoma; EBR = En bloc resection

‡ Not involved in propensity score computation due to 31 missing data

* Not involved in propensity score computation since only informed for the patients with chemotherapy

Table 3 Prognostic factors of local relapse in bivariate and multivariate models based on Fine and Gray sub-distribution hazard function

	Bivariate analysis		Multivariate analysis	
Variable	SHR and 95% CI	*P*	SHR and 95% CI	*P*
Female	1.12 [0.54 ; 2.30]	.764		
Age (yo)≥50	1.52 [0.73 ; 3.19]	.265		
Bone versus Soft tissues	1.71 [0.77 ; 3.77]	.185		
Tumor size ≥5 cm ‡	1.56 [0.62 ; 3.95]	.342		
Deep tumor	1.62 [0.72 ; 3.62]	.244		
Location (versus limb)				
Thorax, abdomen and pelvis	1.71 [0.77;3.79]	.187		
Head and neck	0.71 [0.17;2.96]	.637		
Grade (versus grade 1)				
2	1.72 [0.76 ; 3.91]	.196		
3	1.85 [0.59 ; 5.82]	.292		
EMC	0.32 [0.10 ; 1.02]	.053	0.24 [0.06 ;0.99]	.048
En bloc resection	0.25 [0.12 ; 0.52]	<.001		
Quality of resection R1/R2 versus R0	5.84 [2.37 ; 14.40]	<.001		
Resection (versus R0 with EBR)				
R0 without EBR or R1/2 with EBR	5.41 [1.71 ; 17.12]	.004	7.05 [2.08 ; 23.87]	.002
R1/2 without EBR	12.19[3.82 ; 38.83]	<.001	12.75[3.96 ;41.02]	<.001
Chemotherapy	0.78 [0.24; 2.55]	.676		
Radiotherapy	0.43 [0.19; 1.00]	.050	0.36 [0.14 ;0.88]	.025

Abbreviations: yo = years old; EMC = Extraskeletal Myxoid Chondrosarcoma; EBR = En Bloc Resection; SHR = Sub-distribution Hazard Ratio; CI = Confidence Interval

‡ 31 missing data

Table 4 Prognostic factors of disease-free survival and overall survival by bivariate and multivariate Cox proportional hazard models

Variable	Disease-free survival				Overall survival			
	Bivariate analysis		Multivariate analysis		Bivariate analysis		Multivariate analysis	
	HR and 95%CI	*P*	HR and 95%CI	*P*	HR and 95%CI	*P*	HR and 95%CI	*P*
Female	0.79 [0.49 ; 1.30]	.356			0.66 [0.34;1.27]	.210		
Age ≥50 yo	1.60 [0.97 ; 2.63]	.065			1.74 [0.90;3.35]	.097		
Bone versus Soft tissues	0.70 [0.43 ; 1.15]	.160			0.90 [0.48;1.72]	.761		
Location (versus limb)								
Thorax, abdomen and pelvis	0.87 [0.50;1.51]	.618			0.96 [0.47;1.95]	.904		
Head and neck	0.22 [0.07;0.70]	.011			0.30 [0.07;1.25]	.099		
Tumor size ≥5cm ‡<5	2.55 [1.31 ; 4.93]	.006			3.40 [1.31;8.80]	.012		
Deep tumor	2.30 [1.29 ; 4.10]	.005	3.05 [1.64 ;5.69]	<.001	2.27 [1.04;4.93]	.039	2.41 [1.09 ;5.33]	.030
Grade (versus grade 1)								
2	1.78 [0.99 ; 3.20]	.053	2.32 [1.25 ;4.33]	.008	1.78 [0.99 ; 3.20]	.053	2.69 [1.07 ; 6.81]	.036
3	5.96 [3.09 ; 3.09]	<.001	16.24 [7.09 ;37.20]	<.0001	5.96 [3.09 ; 11.51]	<.001	9.99 [3.85 ; 25.92]	<.001
EMC	0.97 [0.56 ; 1.70]	.929			0.44 [0.19;1.07]	.070	0.33 [0.131;0.80]	.014
En bloc resection	0.47 [0.28 ; 0.81]	.006			1.01 [0.44;2.31]	.979		
Quality of resection R1/R2 versus R0	2.00 [1.21; 3.31]	.007	2.45 [1.45 ;4.13]	<.001	1.53 [0.80;2.95]	.201		
Resection (versus R0 with EBR)								
R0 without EBR or R1/2 with EBR	1.44 [0.80;2.61]	.227			1.59 [0.78;3.23]	.202		
R1/2 without EBR	3.03 [1.59;5.76]	<.001			1.06 [0.36;3.16]	.914		
Chemotherapy	1.33 [0.68;2.62]	.401			2.18 [1.03 ;4.59]	.041		
Radiotherapy	0.68 [0.41; 1.13]	.135	0.25 [0.13;0.45]	<.0001	1.03 [0.55;1.94]	.927		

Abbreviations: yo = years old; EMC = Extraskeletal Myxoid Chondrosarcoma; EBR = En Bloc Resection; HR = Hazard Ratio; CI = Confidence Interval

‡ 31 missing data, not included in multivariate analysis,