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Which Factors Are Associated with Local Control and Survival of Patients with Localized Pelvic Ewing's Sarcoma? A Retrospective Analysis of Data from the Euro-EWING99 Trial

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Abstract

Background Local treatment of pelvic Ewing's sarcoma may be challenging, and intergroup studies have focused on improving systemic treatments rather than prospectively evaluating aspects of local tumor control. The Euro-EWING99 trial provided a substantial number of patients with localized pelvic tumors treated with the same chemotherapy protocol. Because local control included surgical resection, radiation therapy, or a combination of both, we wanted to investigate local control and survival with respect to the local modality in this study cohort.

Questions/purposes (1) Do patients with localized sacral tumors have a lower risk of local recurrence and higher survival compared with patients with localized tumors of the innominate bones? (2) Is the local treatment modality associated with local control and survival in patients with sacral and nonsacral tumors? (3) Which local tumor- and treatment-related factors, such as response to neoadjuvant chemotherapy, institution where the biopsy was performed, and surgical complications, are associated with local recurrence and patient survival in nonsacral tumors? (4) Which factors, such as persistent extraosseous tumor growth after chemotherapy or extent of bony resection, are independently associated with overall survival in patients with bone tumors undergoing surgical treatment?

Methods Between 1998 and 2009, 1411 patients with previously untreated, histologically confirmed Ewing's sarcoma were registered in the German Society for Pediatric Oncology and Hematology Ewing's sarcoma database and treated in the Euro-EWING99 trial. In all, 24% (339 of 1411) of these patients presented with a pelvic primary sarcoma, 47% (159 of 339) of which had macroscopic metastases at diagnosis and were excluded from this analysis. The data from the remaining 180 patients were reviewed retrospectively, based on follow-up data as of July 2016. The median (range) follow-up was 54 months (5 to 191) for all patients and 84 months (11 to 191) for surviving patients. The study endpoints were overall survival, local recurrence and event-free survival probability, which were calculated with the Kaplan-Meier method and compared using the log-rank test. Hazard ratios (HRs) with their respective 95% CIs were estimated in a multivariate Cox regression model.

Results Sacral tumors were associated with a reduced probability of local recurrence (12% [95% CI 1 to 22] versus 28% [95% CI 20 to 36] at 5 years, p = 0.032), a higher event-free survival probability (66% [95% CI 51 to 81] versus 50% [95% CI 41 to 58] at 5 years, p = 0.026) and a higher overall survival probability (72% [95% CI 57 to 87] versus 56% [95% CI 47 to 64] at 5 years, p = 0.025) compared with nonsacral tumors. With the numbers available, we found no differences between patients with sacral tumors who underwent definitive radiotherapy and those who underwent combined surgery and radiotherapy in terms of local recurrence (17% [95% CI 0 to 34] versus

0% [95% CI 0 to 20] at 5 years, p = 0.125) and overall survival probability (73% [95% CI 52 to 94] versus 78% [95% CI 56 to 99] at 5 years, p = 0.764). In nonsacral tumors, combined local treatment was associated with a lower local recurrence probability (14% [95% CI 5 to 23] versus 33% [95% CI 19 to 47] at 5 years, p = 0.015) and a higher overall survival probability (72% [95% CI 61 to 83] versus 47% [95% CI 33 to 62] at 5 years, p = 0.024) compared with surgery alone. Even in a subgroup of patients with wide surgical margins and a good histologic response to induction treatment, the combined local treatment was associated with a higher overall survival probability (87% [95% CI 74 to 100] versus 51% [95% CI 33 to 69] at 5 years, p = 0.009), compared with surgery alone.
A poor histologic response to induction chemotherapy in nonsacral tumors (39% [95% CI 19 to 59] versus 64% [95% CI 52 to 76] at 5 years, p = 0.014) and the development of surgical complications after tumor resection (35% [95% CI 11 to 59] versus 68% [95% CI 58 to 78] at 5 years, p = 0.004) were associated with a lower overall survival probability in nonsacral tumors, while a tumor biopsy performed at the same institution where the tumor resection was performed was associated with lower local recurrence probability (14% [95% CI 4 to 24] versus 32% [95% CI 16 to 48] at 5 years, p = 0.035), respectively.
In patients with bone tumors who underwent surgical treatment, we found that after controlling for tumor localization in the pelvis, tumor volume, and surgical margin status, patients who did not undergo complete (defined as a Type I/II resection for iliac bone tumors, a Type II/III resection for pubic bone and ischium tumors and a Type I/II/III resection for tumors involving the acetabulum, according to

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the Enneking classification) removal of the affected bone (HR 5.04 [95% CI 2.07 to 12.24]; p < 0.001), patients with a poor histologic response to induction chemotherapy (HR 3.72 [95% CI 1.51 to 9.21]; p = 0.004), and patients who did not receive additional radiotherapy (HR 4.34 [95% CI 1.71 to 11.05]; p = 0.002) had a higher risk of death. The analysis suggested that the same might be the case in patients with a persistent extraosseous tumor extension after induction chemotherapy (HR 4.61 [95% CI 1.03 to 20.67]; p = 0.046), although the wide CIs pointing at a possible sparse-data bias precluded any definitive conclusions.

Conclusion Patients with sacral Ewing's sarcoma appear to have a lower probability for local recurrence and a higher overall survival probability compared with patients with tumors of the innominate bones. Our results seem to support a recent recommendation of the Scandinavian Sarcoma Group to locally treat most sacral Ewing's sarcomas with definitive radiotherapy. Combined surgical resection and radiotherapy appear to be associated with a higher overall survival probability in nonsacral tumors compared with surgery alone, even in patients with a wide resection and a good histologic response to neoadjuvant chemotherapy. Complete removal of the involved bone, as defined above, in patients with nonsacral tumors may be associated with a decreased likelihood of local recurrence and improved overall survival. Persistent extraosseous tumor growth after induction treatment in patients with nonsacral bone tumors undergoing surgical treatment might be an important indicator of poorer overall survival probability, but the possibility of sparse-data bias in our cohort means that this factor should first be validated in future studies.

Level of Evidence Level III, therapeutic study.

Introduction

Approximately 20% of all Ewing's sarcomas are located in the pelvis [3, 29]. Local symptoms tend to manifest late in the disease course, and at the time of diagnosis tumors in the pelvis often have a larger volume than tumors in other sites such as the extremities, they present more commonly with primary metastases, and they have a poorer overall survival [13, 21, 28]. Local treatment is often challenging because tumor resection with wide surgical margins can be difficult to achieve, while surgical procedures and local radiotherapy are both associated with considerable morbidity owing to the proximity of important anatomic structures [14, 16].

Although local treatment of the primary tumor is essential for long-term survival in patients with Ewing's sarcoma [3], studies have focused on improving systemic treatments rather than prospectively evaluating aspects of local tumor control, with the exception of two small trials [4, 25] that examined the impact of different radiotherapy regimens [10]. Randomized controlled trials on local control are generally considered infeasible, and recommendations regarding local treatment are based on the results of observational studies, which mainly compare surgery with radiotherapy, rather than evaluate different surgical approaches [10, 26, 29]. Regarding the particular location of pelvic tumors, a recent retrospective analysis from the Scandinavian Sarcoma Group suggested that both the local treatment and the survival of sacral Ewing's sarcomas differ greatly from nonsacral pelvic tumors [14]. However, available studies are small, include patients treated with different chemotherapy protocols, and have produced low-quality evidence and sometimes conflicting results [14, 16, 26]. This has led to divergent treatment recommendations concerning the role of surgery and radiotherapy for local control, and the effect of several aspects of local treatment has yet to be examined [5, 14, 17].

To look at these issues in a more rigorous fashion, we performed a retrospective analysis of patients with localized pelvic Ewing's sarcoma treated in the Euro-EWING99 trial, a large international prospective randomized study comparing the impact of different consolidation regimens on patient survival after a uniform induction chemotherapy and surgery, radiotherapy or a combination of both as local treatment. While the primary and secondary endpoints of the study did not examine aspects of local control, it did provide a large dataset of patients treated with the same induction chemotherapy protocol, allowing an evaluation of the impact of tumor-related factors and local treatment on local recurrence and patient survival in relatively large and fairly homogeneous patient groups.

We therefore asked: (1) Do patients with localized sacral tumors have a lower risk of local recurrence and higher survival compared with patients with localized tumors of the innominate bones? (2) Is the local treatment modality associated with local control and survival in patients with sacral and nonsacral tumors? (3) Which local tumor- and treatment-related factors, such as response to neoadjuvant chemotherapy, the institution where the biopsy was performed, and surgical complications, are associated with local recurrence and patient survival in nonsacral tumors? (4) Which factors, such as persistent extraosseous tumor growth after chemotherapy or extent of bony resection, are independently associated with overall survival in patients with bone tumors undergoing surgical treatment?

Patients and Methods

Between 1998 and 2009, 1411 patients with previously untreated, histologically confirmed Ewing's sarcoma were registered in the German Society for Pediatric Oncology and Hematology Ewing's sarcoma database from institutions in Germany, Austria, Belgium, the Czech Republic, the Netherlands, and Switzerland and treated in the

Euro-EWING99 trial (NCT00020566). In all, 24% (339 of 1411) of these patients presented with a pelvic primary sarcoma. Given the great impact of primary metastases on both local treatment planning and patient prognosis, we decided to focus this analysis on patients with localized disease at presentation only and excluded 47% (159 of 339) of patients with macroscopic metastases at diagnosis, which left 180 patients for evaluation in this study. Given that data relating to at least some of the questions we asked were available for all patients, patients with missing data were therefore only excluded from the analyses of the respective variables. The median (range) follow-up duration was 54 months (5 to 191) for all patients and 84 months (11 to 191) for surviving patients. Only five surviving patients had a follow-up of less than 2 years.

The details of the treatment protocol have been described elsewhere [19, 20]. Briefly, the Euro-EWING99 protocol prescribed six courses of induction chemotherapy with vincristine, ifosfamide, doxorubicin, and etoposide (VIDE) for all patients and consolidation chemotherapy, which depended on risk stratification – based on histological tumor response to neoadjuvant chemotherapy and primary tumor volume for patients with localized disease – and patient randomization. Local treatment was recommended following induction chemotherapy and was based on patient and tumor characteristics [20]. Surgical resection of the primary tumor with wide margins was recommended, when feasible, while definitive radiotherapy with a dose of 54 Gy to 64 Gy was recommended when a wide resection was deemed infeasible, mutilating, or associated with a high risk for severe complications. Preoperative radiotherapy (with a 54 Gy dose) was conducted in patients with a poor clinical response to induction chemotherapy or patients at risk of marginal or intralesional resections, while postoperative radiotherapy (with a 45 Gy to 54 Gy dose) was recommended when wide surgical margins were not achieved and advised in patients with poor histological response to induction treatment (≥ 10% viable tumor cells) [18]. The study protocol was approved by the appropriate local or national ethics committees, institutional review boards, and legal authorities. Informed consent was obtained from all patients and/or their legal guardians according to the Declaration of Helsinki and national guidelines [19].

Table 1. Patient demographics and baseline tumor characteristics

Variable	Number	Percent
Eligible patients	**180**	**100**
Country		
Germany	134	74
Netherlands	17	10
Austria	13	7
Switzerland	9	5
Belgium	4	2
Czech Republic	3	2
Sex		
Male	102	57
Female	78	43
Tumor origin		
Osseous lesion with or without soft-tissue component	158	88
Extraosseous lesion (no bone involvement)	22	12
Tumor site		
Iliac bone	86	48
Ischiopubic bone	28	16
Acetabulum	4	2
Sacrum	40	22
Pelvic soft tissue	6	3
Buttock	7	4
Hip or inguinal region	4	2
Other soft tissue	5	3
Tumor volume		
< 200 mL	79	44
≥ 200 mL	95	53
Unknown	6	3
Locoregional lesions		
None	155	86
Intraspinal extension	18	10
Skip lesions	4	2
Adjacent lymph node involvement	3	2

Data Collection

Data concerning patient demographics (Table 1), tumor characteristics, first-line treatment, and follow-up were collected, coded, and entered into an electronic database. Furthermore, the study records of all 180 patients were reviewed, and missing or inaccurately documented data as well as further details regarding tumor characteristics and primary treatment were collected retrospectively from primary source data available at the study office.

Study Population and Primary Treatment

The median (range) age at the time of diagnosis was 17 years (0.02 to 60). An estimate of the absolute tumor volume was available for 98 patients and ranged from 3 mL to 2836 mL (median 295 mL). Overall, 44% of patients (79 of 180) had a tumor volume at diagnosis < 200 mL, 53% (95 of 180) a volume of ≥ 200 mL, while no data on

categorized tumor volume were available for 3% (six of 180) of patients. All patients with bone tumors had a soft-tissue component at the time of diagnosis. A primary extraosseous lesion (Table 1) was defined in the protocol as a tumor with no bone involvement.

A total of 73% (131 of 180) of patients underwent surgical resection of the primary tumor. Of these procedures, 11% (14 of 131) were unplanned resections before induction chemotherapy and involved both bone (eight of 14) and extraosseous (six of 14) lesions. Most of the surgical procedures were limb-sparing. Only 2% of patients (three of 131) underwent external hemipelvectomy. Fifty-four percent of patients (63 of 117) underwent surgical treatment after induction chemotherapy at the same institution where the tumor biopsy was performed. Thirty-three percent of patients (39 of 117) were surgically treated at a different institution, and 13% of patients (15 of 117) had no data available on where the biopsy was performed. Seventy percent of patients (92 of 131) had wide surgical margins, 11% of patients (14 of 131) had marginal surgical margins, 17% of patients (22 of 131) had intralesional surgical margins, and 2% of patients (3 of 131) had no data available about margin status. Fifteen percent of patients (19 of 131) developed postoperative complications.

A total of 36% of patients (40 of 112) with bone tumors underwent complete removal of the involved bone, defined as a Type I/II resection for iliac bone tumors, a Type II/III resection for pubic bone and ischium tumors, a Type I/II/III resection for tumors involving the acetabulum, or a complete Type IV resection for sacral tumors, according to the Enneking classification [6]. For nonsacral tumors crossing the sacroiliac joint, we applied this term only to the extent of resection of the innominate bones, as no complete sacrectomies were performed in these patients. In all, 60% of patients (67 of 112) underwent an incomplete resection of the involved bone (for example, Type I resection only for iliac bone tumors or Type III resection for pubic bone and ischium tumors), and no data were available for 4% of patients (five of 112). Among the patients with bone tumors who underwent surgical treatment after induction chemotherapy, the extraosseous tumor component had completely decreased in 16% of patients (17 of 104) and was still detectable in 66% of patients (69 of 104); no data about the soft-tissue component of the tumor were available for 17% of patients (18 of 104).

In addition to surgical treatment, 60% of patients (78 of 131) underwent radiotherapy of the primary tumor area. Of these patients, 15% (12 of 78) had preoperative radiotherapy, 79% (62 of 78) had postoperative radiotherapy, and 5% (four of 78) had no data available on the timing of radiation treatment. Definitive radiotherapy as the sole local treatment modality was performed in 22% of patients (40 of 180), and 5% of patients (nine of 180) did not undergo any local treatment.

We evaluated histologic response to induction chemotherapy only in patients who underwent surgery after neoadjuvant chemotherapy and did not receive preoperative radiation treatment. Among those patients, 69% (72 of 105) had a good response to induction chemotherapy, defined as $< 10\%$ vital tumor cells, and 23% (24 of 105) had a poor response, with $\geq 10\%$ vital tumor cells [25]. The histologic response could not be determined in 4% of patients (four of 105) who underwent re-excision of the tumor bed after primary incomplete resection, in 2% of patients (two of 105) who received extracorporeal irradiation and replantation of the affected bone, and in 1% of patients (one of 105) who underwent incomplete tumor resection; no data on the histologic response were available for 2% of patients (two of 105).

The probability of local recurrence at 2 years was 19% and 24% at 5 years. The probability of event-free survival was 64% after 2 years and 53% after 5 years, and the probability of overall survival was 81% at 2 years and 59% at 5 years.

Study Outcomes and Statistical Analyses

Our primary study outcome of interest was overall survival probability, while our secondary outcomes of interest were local recurrence probability and event-free survival probability. All three outcomes were calculated with the Kaplan-Meier method, and survival curves were compared with the log-rank test. The duration of follow-up and time to event (disease progression, locoregional recurrence, distant metastasis, secondary malignancy, or death of any cause) were calculated from the date of diagnostic biopsy. Local or systemic disease progression during treatment was classified as a local or systemic recurrence for this analysis. We used receiver operating characteristic curves to analyze the accuracy of continuous variables in predicting events. Area under the curve values were calculated using a nonparametric distribution assumption. We analyzed contingency tables with Fisher's exact test. Continuous variables were checked for normality using the Shapiro-Wilk test. Nonparametric analyses were performed with the Mann-Whitney U test.

The survival analysis was based on follow-up data as of July 2016 [27]. Hazard ratios (HRs) with their respective 95% CIs were estimated in a multivariate Cox regression model. Because known important prognostic factors (such as histological response to neoadjuvant chemotherapy) were only available for subgroups of patients (for example, patients who underwent surgery without previous radiotherapy), and the number of factors that can be included in a multivariate model depend on the number of observed events, we chose to only perform a multivariate analysis of independent factors for overall survival in patients who underwent surgical treatment. We included factors

associated with overall survival in univariate analysis in the model, as well as tumor volume, which has previously been proposed as a prognostic factor in Ewing's sarcoma but has not been examined in patients with localized pelvic disease only. Statistical calculations were performed with IBM SPSS statistics software version 21.0 (IBM Corp, Armonk, NY, USA). All p values were two-sided; a p value < 0.05 was considered significant.

Results

Do Patients with Localized Sacral Tumors Have a Lower Risk of Local Recurrence and Higher Survival Compared with Patients with Localized Tumors of the Innominate Bones?

Sacral tumors were associated with a reduced probability for local recurrence (12% [95% CI 1 to 22] versus 28% [95% CI 20 to 36] at 5 years, p = 0.032), a higher event-free survival probability (66% [95% CI 51 to 81] versus 50% [95% CI 41 to 58] at 5 years, p = 0.026) and a higher overall survival probability (72% [95% CI 57 to 87] versus 56% [95% CI 47 to 64] at 5 years, p = 0.025) compared with nonsacral pelvic tumors.

Is the Local Treatment Modality Associated with Local Control and Survival in Patients with Sacral and Nonsacral Tumors?

With the numbers available, we found no differences between patients with sacral tumors who underwent definitive radiotherapy and those who underwent combined surgery and radiotherapy in terms of local recurrence (17% [95% CI 0 to 34] versus 0% [95% CI 0 to 20] at 5 years, p = 0.125) and overall survival probability (73% [95% CI 52 to 94] versus 78% [95% CI 56 to 99] at 5 years, p = 0.764). In nonsacral tumors, combined local treatment was associated with a lower (Fig. 1A) local recurrence probability (14% [95% CI 5 to 23] versus 33% [95% CI 19 to 47] at 5 years, p = 0.015) and a higher (Fig. 1B) overall survival probability (72% [95% CI 61 to 83] versus 47% [95% CI 33 to 62] at 5 years, p = 0.024) compared with surgery alone. Even in a subgroup of patients with wide surgical margins and a good histologic response to induction treatment, the combined local treatment was associated with a higher overall survival probability (87% [95% CI 74 to 100] versus 51% [95% CI 33 to 69] at 5 years, p = 0.009) and a higher event-free survival probability (83% [95% CI 68 to 98] versus 42% [95% CI 24 to 60] at 5 years, p = 0.015), compared with surgery alone. With the low numbers of available patients who underwent definitive radiotherapy, we were only able to show (Table 2) that definitive radiotherapy for nonsacral tumors was associated with a higher local recurrence probability (40% [95% CI 15 to 65] versus 14% [95% CI 5 to 23], p = 0.018), compared with combined surgery and radiation treatment.

Which Local Tumor- and Treatment-related Factors are Associated with Local Recurrence and Patient Survival in Nonsacral Tumors?

Tumor volume, with a cutoff value of 200 mL, was not associated with local recurrence, event-free survival, and

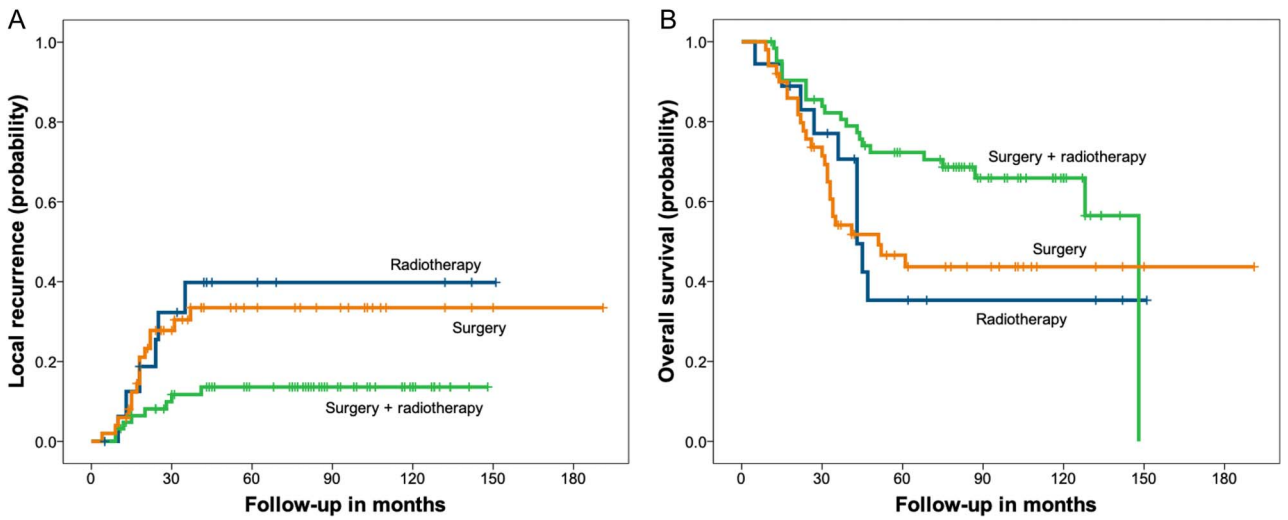

Fig. 1 A-B This figure shows the probability of (**A**) local recurrence and (**B**) overall survival of patients with nonsacral tumors according to the local treatment modality.

overall survival in this group of patients with localized nonsacral Ewing's sarcoma (Table 2). The receiver operating characteristic curve analysis confirmed that the absolute tumor volume was also not associated with local recurrence (area under the curve 0.584; p = 0.213), event-free survival (area under the curve 0.581; p = 0.171), or overall survival (area under the curve 0.565; p = 0.269). On the other hand, a poor histologic response to induction chemotherapy (39% [95% CI 19 to 59] versus 64% [95% CI 52 to 76] at 5 years, p = 0.014) and the development of surgical complications after tumor resection (35% [95% CI 11 to 59] versus 68% [95% CI 58 to 78] at 5 years, p = 0.004) were associated with poorer overall survival probability (Table 2). A tumor biopsy performed at the same institution where the tumor resection was performed was associated with a lower local recurrence probability (14% [95% CI 4 to 24] versus 32% [95% CI 16 to 48] at 5 years, p = 0.035) (Table 2).

A persistent extraosseous tumor component after induction treatment in patients with nonsacral bone tumors who underwent surgical treatment was associated with a higher local recurrence probability (26% [95% CI 12 to 40] versus 0% [95% CI 0 to 18] at 5 years, p = 0.026), lower event-free probability (37% [95% CI 25 to 49] versus 80% [95% CI 59 to 100] at 5 years, p = 0.031), and overall survival probability (48% [95% CI 35 to 61] versus 86% [95% CI 68 to 100] at 5 years, p = 0.005) (Table 2). Postoperative radiotherapy in nonsacral tumors with a persistent extraosseous component was associated with better overall survival probability (61% [95% CI 44 to 78] versus 28% [95% CI 10 to 46] at 5 years, p = 0.038), but, with the number of patients available for this subgroup analysis (n = 55), we could not show differences in local recurrence (21% [95% CI 6 to 36] versus 42% [95% CI 21 to 63] at 5 years, p = 0.092) or event-free survival probability 48% [95% CI 30 to 66] versus 26% [95% CI 8 to 44] at 5 years, p = 0.174).

Finally, complete removal of the affected bone, as defined above, was associated with a reduced probability of local recurrence (6% [95% CI 2 to 14] versus 35% [95% CI 21 to 49] at 5 years, p = 0.001) (Fig. 2A), event-free survival (69% [95% CI 54 to 84] versus 38% [95% CI 24 to 52] at 5 years, p = 0.003), and overall survival (83% [95% CI 71 to 95] versus 44% [95% CI 30 to 58] at 5 years, p < 0.001) (Fig. 2B) in patients with nonsacral tumors (Table 2). A subgroup analysis of patients with wide or radical surgical margins confirmed the association of complete removal of the affected bone and lower local recurrence (7% [95% CI 0 to 15] versus 28% [95% CI 13 to 43] at 5 years, p = 0.017), higher event-free survival (72% [95% CI 56 to 87] versus 41% [95% CI 25 to 58] at 5 years, p = 0.028), and higher overall survival probability (81% [95% CI 67 to 95] versus 50% [95% CI 34 to 66] at 5 years, p = 0.001). With the numbers we had, we could show no differences in the median (range) tumor volume (389 mL [127 to 1244] versus 350 mL [39 to 1435], p = 0.679) or the proportion of patients with a poor histologic response to neoadjuvant treatment (17% [6 of 36] versus 31% [15 of 48], p = 0.202) and persistent extraosseous tumor extent after induction treatment (71% [22 of 31] versus 86% [36 of 45], p = 0.281) between patients who underwent complete removal of the affected bone and those with incomplete removal.

Which Factors Are Independently Associated with Overall Survival in Patients with Bone Tumors Undergoing Surgical Treatment?

After controlling for tumor localization in the pelvis, tumor volume, and surgical margin status, we found that patients who did not undergo complete removal of the affected bone as defined above, (HR 5.04 [95% CI 2.07 to 12.24]; p < 0.001), patients with a poor histologic response to induction chemotherapy (HR 3.72 [95% CI 1.51 to 9.21]; p = 0.004), and patients who did not receive additional radiotherapy (HR 4.34 [95% CI 1.71 to 11.05]; p = 0.002) had a higher risk of death (Table 3). The analysis suggested that the same might be the case for patients with a persistent extraosseous tumor growth after induction chemotherapy (HR 4.61 [95% CI 1.03 to 20.67]; p = 0.046), although the wide confidence intervals pointing at a possible sparse-data bias precluded any definitive conclusions.

Discussion

The most appropriate local treatment of patients with pelvic Ewing's sarcoma has been the subject of many observational studies, which mainly focused on the comparison between surgery and radiotherapy. The conflicting results of these studies have been attributed to different criteria influencing the choice and outcome of each local treatment modality, such as tumor size, the presence of metastases, clinical response to chemotherapy, and surgical resectability [5, 16, 29]. Our analysis of a large, international dataset of patients treated with the same chemotherapy protocol found that patients with sacral tumors had a reduced local recurrence probability and a higher event-free and overall survival probability compared with patients with tumors of the innominate bones. We also showed for patients with nonsacral pelvic tumors that surgical resection combined with radiation therapy is associated with higher local control and overall survival probabilities, and that the complete removal of the affected bone is associated with a better overall survival.

Table 2. The probabilities of local recurrence, event-free survival and overall survival at 5 years for patients with nonsacral tumors, with the respective standard errors, as calculated with the Kaplan-Meier method and compared with the log-rank test

			5-year local recurrence			5-year event-free survival			5-year overall survival		
Variable	Number	Percent	Percent	Standard error	p value	Percent	Standard error	p value	Percent	Standard error	p value
Eligible patients	140	100	28	4.0		50	4.3		56	4.3	
Age											
≤ 15 years	59	42	21	5.7	0.091	56	6.7	0.192	66	6.3	0.047
> 15 years	81	58	33	5.5		46	5.6		48	5.8	
Sex											
Male	79	56	34	5.5	0.060	43	5.7	0.091	48	5.8	0.128
Female	61	44	21	5.6		59	6.5		66	6.3	
Tumor origin											
Osseous lesion	118	84	27	4.3	0.503	47	4.7	0.093	55	4.7	0.546
Extraosseous lesion	22	16	34	10.5		66	10.5		61	11.0	
Primary tumor volume											
< 200 mL	52	38	25	6.4	0.496	52	7.2	0.707	54	7.3	0.907
≥ 200 mL	85	62	30	5.2		47	5.5		56	5.5	
Locoregional extension											
No	131	94	27	4.1	0.500	50	4.5	0.523	56	4.5	0.985
Yes	9	6	41	18.5		39	17.3		50	17.7	
Surgical treatment or biopsy											
Same institution	57	61	14	4.9	0.035	62	6.6	0.094	65	6.5	0.246
Different institution	36	39	32	8.0		39	8.5		54	8.5	
Removal of involved bone											
Complete	37	42	6	4.0	0.001	69	7.8	0.003	83	6.3	< 0.001
Incomplete	52	58	35	7.2		38	6.9		44	7.1	
Surgical margin width											
Wide or radical	87	79	17	4.2	0.386	58	5.5	0.839	65	5.3	0.874
Marginal	11	10	29	14.3	0.147	55	15.0	0.043	64	14.5	0.043
Intralesional	12	11	55	18.1		20	12.4		28	13.5	
Wide or radical versus intralesional					0.001			0.001			0.001
Histologic response											
< 10% vital tumor	65	74	23	5.5	0.237	58	6.3	0.017	64	6.2	0.014
≥ 10% vital tumor	23	26	34	10.7		31	10.2		39	10.2	
Surgical complications											
No	82	83	21	4.6	0.760	60	5.6	0.017	68	5.3	0.004
Yes	17	17	12	7.8		26	12.1		35	12.4	
Soft-tissue infiltration at surgery (bone tumors)											
No	17	22	0		0.026	80	10.7	0.031	86	9.3	0.005
Yes	60	78	28	6.1		37	6.3		48	6.5	

Table 2. continued

Variable	Number	Percent	5-year local recurrence			5-year event-free survival			5-year overall survival		
			Percent	Standard error	p value	Percent	Standard error	p value	Percent	Standard error	p value
Local treatment modality											
Surgery and radiotherapy	63	45	14	4.5	0.015	63	6.2	0.077	72	5.7	0.024
Surgery	50	36	33	7.2	0.758	43	7.3	0.812	47	7.4	0.988
Radiotherapy	18	13	40	12.8		42	12.2		35	12.5	
None	9	6	85	13.3	< 0.001	11	10.5	0.004	22	13.9	0.055
Surgery and radiotherapy versus radiotherapy					0.018			0.150			0.074

Limitations

Our study has several limitations. To limit a possible omitted-variable bias, we performed many analyses with various subsets of the data across many variables, leading to a potentially inflated Type 1 error. Some of these subsets were small – especially accounting for the missing data for each variable – resulting in possible Type 2 errors. Furthermore, the observational nature of this analysis meant that adequate patient numbers may have been lacking some combinations of risk factors and investigated outcomes in our cohort, leading to possible sparse-data bias [12, 22], which is highlighted by the very wide confidence intervals of the persistent extraosseous tumor component in our multivariate Cox regression model, which ranged from just above one to a dramatically high HR (Table 3).

Although these limitations mean that some of our results should be interpreted with caution and underline the need for validation in separate cohorts, we also believe that they are partly offset by our strict inclusion criteria of patients with localized disease at presentation only treated with a single induction chemotherapy protocol. What is more, the fact that this large patient cohort was acquired over 12 years from centers in six European countries that contribute to one of the largest international prospective randomized studies for Ewing's sarcoma patients reflects the very low incidence of Ewing's sarcoma, its heterogeneity at presentation, and the difficulty of evaluating aspects of local

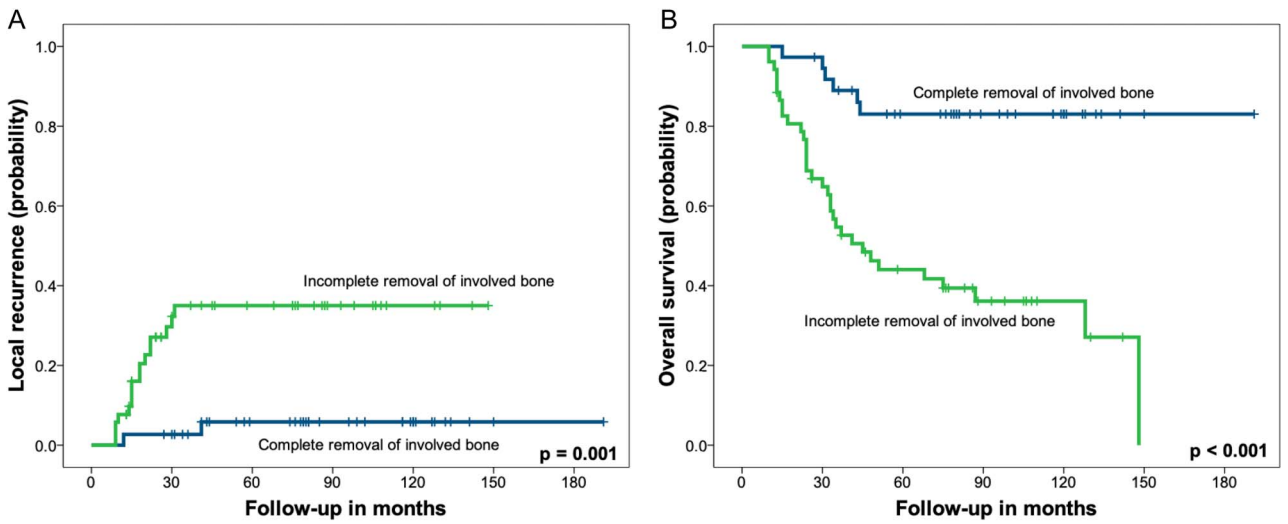

Fig. 2 A-B The probability of (**A**) local recurrence and (**B**) overall survival of patients with nonsacral tumors of the bone is depicted according to removal of the involved bone.

Table 3. Multivariate analysis with the Cox proportional hazards model of overall survival in patients with bone tumors who underwent surgical treatment

Factor	Hazard ratio	95% CI	p value
Tumor location			
Nonsacrum (vs sacrum)	1.92	0.46 to 7.92	0.370
Primary tumor volume			
≥ 200 mL (vs < 200 mL)	1.79	0.75 to 4.28	0.193
Removal of involved bone			
Incomplete (vs complete)	5.04	2.07 to 12.24	< 0.001
Histologic response			
≥ 10% vital tumor (vs < 10% vital tumor)	3.72	1.51 to 9.12	0.004
Surgical margins			
Marginal (vs wide or radical)	0.82	0.29 to 2.35	0.713
Intralesional (vs wide or radical)	4.35	1.17 to 16.25	0.029
Local treatment modality			
Surgery (vs surgery and radiotherapy)	4.34	1.71 to 11.05	0.002
Persisting extraosseous tumor component at surgery			
Yes (vs no)	4.61	1.03 to 20.67	0.046

tumor growth and local treatment. We believe that, in the absence of prospective randomized data – which are unlikely to become available in the foreseeable future – the rigor of our analysis contributes to the available reports of others and provides quality data for clinicians consulting patients on local treatment and researchers planning future studies.

We also acknowledge that the large time period over which patients were recruited and the fact that patients were treated in a large number of institutions across Europe may have caused some heterogeneity in our cohort, especially regarding local treatment indications and radiotherapy techniques. The indications for surgical intervention likely varied to some extent from site to site, and some centers treated more patients and were likely more experienced than others. On the other hand, aside from the local treatment recommendations in the study protocol that are described above, the Euro-EWING99 trial also offered central guidance for local therapy planning that was based on interdisciplinary tumor board discussions in the coordinating data center, for which local imaging was available. This central guidance was regularly performed for patients with pelvic tumors.

Do Patients with Localized Sacral Tumors Have a Lower Risk of Local Recurrence and Higher Survival Compared with Patients with Localized Tumors of the Innominate Bones?

Our data confirm that sacral tumors are associated with a lower probability for local recurrence and a better event-free and overall survival compared with nonsacral pelvic Ewing's tumors. Although a sacral tumor location was not associated with overall survival in patients undergoing surgical treatment (Table 3), most patients with sacral tumors underwent definitive radiotherapy and could not be included in the model. The relevance of the exact anatomic location of a Ewing's sarcoma in the pelvis was first reported in a recent retrospective analysis from the Scandinavian Sarcoma group [14]. One possible explanation for the better survival of sacral tumors may be that the high vascularization of sacral tumors may have a positive influence in tumor response to chemotherapy and radiation treatment.

Is the Local Treatment Modality Associated with Local Control and Survival in Patients with Sacral and Nonsacral Tumors?

The combination of surgery and radiotherapy was associated with better local and systemic disease control and a lower risk for death compared with surgery alone in patients with nonsacral tumors. Postoperative radiotherapy is usually recommended for patients with microscopically or macroscopically incomplete surgical resections or a poor histologic response to induction chemotherapy [7, 18]. However, our study demonstrated a benefit in terms of overall survival in patients who undergo adjuvant radiotherapy for nonsacral pelvic tumors, even after surgical treatment with wide margins and a good histologic response to neoadjuvant chemotherapy, although it should be noted that the morbidity of the combined treatment is greater than the morbidity of surgery and radiotherapy alone, something future studies should evaluate prospectively. Foulon et al. [9] recently analyzed 599 patients with localized Ewing's sarcoma of the appendicular and axial skeleton who were treated in the Euro-EWING99 trial and who had a good histologic response after neoadjuvant chemotherapy. They also found a reduction in local recurrence in patients who received postoperative radiotherapy, with no differences in event-free survival and overall survival. The Euro-EWING99 protocol's recommendation for surgical resection of the primary tumor with

wide margins, when feasible, and the low proportion of patients with nonsacral tumors treated only with radiotherapy preclude definitive conclusions regarding the role of this modality in the treatment of nonsacral pelvic Ewing's sarcoma. On the other hand, with the numbers available, we found no differences between definitive radiotherapy and combined surgery and radiotherapy in terms of local recurrence, event-free survival, and overall survival in patients with sacral tumors. The Scandinavian Sarcoma Group reported on similar findings and suggested that definitive radiotherapy may be the local treatment modality of choice for patients with sacral tumors [14]. In an early combined analysis of all patients with sacral and nonsacral tumors in our cohort, combined local treatment was associated with improved local recurrence but not event-free survival and overall survival compared with definitive radiotherapy (data not shown), which might lead to the assumption that definitive radiotherapy is an adequate local treatment modality for all pelvic Ewing's sarcomas. Similar data were reported by the Children's Oncology Group in a retrospective evaluation of 75 patients with localized pelvic Ewing's sarcoma treated in the INT-0091 trial [29]. The authors of that report concluded that the local control measure, when used according to the treating physician's best judgment, had no impact on the survival of patients with pelvic Ewing's sarcoma. However, their analysis did not differentiate sacral and nonsacral tumors. In light of our results and the results of the Scandinavian Sarcoma Group's study, we believe sacral tumors should be evaluated separately from tumors in the innominate bones in future studies, especially those examining the result of local treatment modalities.

What Other Local Tumor- and Treatment-related Factors Are Associated with Local Recurrence and Patient Survival in Nonsacral Tumors?

Our analysis demonstrated that a poor histologic response to induction chemotherapy and the development of surgical complications were associated with a lower overall survival in patients with nonsacral tumors, whereas performing the tumor biopsy at the same institution where the tumor resection was performed was associated with a lower local recurrence probability. The correlation of histologic response to induction chemotherapy and patient survival has long been recognized in Ewing's sarcoma [25], and prospective randomized trials have used this parameter for patient stratification [27]. Biopsies at referring institutions that did not perform the surgical tumor resection have previously been associated with a higher rate of complications, treatment delays and more extensive surgical resections; an analysis by the Cooperative Osteosarcoma Study Group also found a higher local recurrence probability in patients who underwent a biopsy at a referring institution [2, 23]. Our results confirm the potential benefit of referring a patient with a suspected Ewing's sarcoma to an institution capable of performing definitive local treatment before tumor biopsy.

Which Factors Are Independently Associated with Overall Survival in Patients with Bone Tumors Undergoing Surgical Treatment With or Without Postoperative Radiotherapy?

The complete removal of the involved bone and the disappearance of the extraosseous tumor component were associated with a lower risk for death in our multivariate Cox regression model. Both findings should be interpreted with caution. Regarding the complete removal of the involved bone, for this analysis, we were unable to review the pelvic MRIs of all patients at diagnosis and before surgery. Ewing's sarcoma is known to shrink under induction treatment, and current guidelines recommend that surgical resection should include all anatomic structures involved in the original pretreatment tumor extension, when feasible [11]. Therefore, one possible reason for our findings might be that wide resection with incomplete removal of the involved bone did not always encompass the initial tumor extension. On the other hand, a small study on different radiotherapy fields for the local treatment of Ewing's sarcoma has shown that radiation fields involving the whole affected bone could be substituted with smaller fields without affecting survival, if these fields covered the initial extent of the tumor with an additional margin of at least 2 cm [4]. Although a surgical margin width of at least 2 cm in the affected bone is easy to achieve in the long bones, it is much more difficult to attain in flat bones such as the pelvis, if the bone is only partially excised. As to the possible reasons for this result, we can only speculate. One possibility is that microfoci of Ewing's sarcoma extend beyond the main tumor component depicted on MRI. It has been suggested that residual viable tumor cells at the primary tumor site may be responsible for the development of secondary metastases, even in the absence of clinically or radiologically apparent local recurrence [24]. Given the poorer functional result that more aggressive resections generally lead to, this finding will need to be validated in a separate patient cohort. Regarding the impact of a persistent extraosseous component, the wide confidence intervals point to a possible sparse-data bias. However, soft tissue invasion by the primary tumor at the time of diagnosis has been associated with poorer patient survival, while changes in the tumor volume after induction treatment have been shown to correlate with the histologic response to neoadjuvant chemotherapy [1, 8]. The need for an accurate, noninvasive assessment of the tumor response

after induction treatment has led to evaluation with sequential whole-body 18F fluorodeoxyglucose-positron emission tomography/CT in recent prospective studies [7, 10, 11]. Considering the high radiation doses associated with sequential positron emission tomography/CT and the associated risk of secondary malignancies [15], as well as the cost of scanning, we propose that future studies should also prospectively evaluate whether the presence of a persistent extraosseous tumor component after induction treatment can act as a simple, cost-effective, and ionizing radiation-free surrogate marker for overall survival.

Conclusions

Patients with sacral Ewing's sarcoma appear to have a lower probability for local recurrence and a higher overall survival probability compared with patients with tumors of the innominate bones. Our results seem to support a recent recommendation of the Scandinavian Sarcoma Group to locally treat most sacral Ewing's sarcomas with definitive radiotherapy. On the other hand, combined surgery and radiotherapy may be associated with a higher overall survival probability compared with surgery alone in patients with nonsacral pelvic tumors, even in patients with a wide resection and a good histologic response to neoadjuvant chemotherapy. Patients undergoing surgical treatment should undergo biopsy at the institution where definitive surgery is planned. A persistent extraosseous tumor extension after induction treatment in patients with nonsacral bone tumors undergoing surgical treatment might be an important indicator of poorer overall survival probability, but the possibility of sparse-data bias in our cohort means that this factor should first be validated in future studies. Finally, complete removal of the involved bone, as defined above, in patients with nonsacral tumors was associated with a decreased likelihood of local recurrence and a higher overall survival probability in our analysis. Because of the observational nature of our study and the impact this parameter might have on the extent of surgical treatment of nonsacral pelvic Ewing's sarcoma and the functional result after treatment, we plan to validate this finding in a separate patient cohort.

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