Personalised medicine for multiple outcomes : methods and application

Rüten-Budde, A.J.

CHAPTER 8

Individual risk evaluation for local recurrence and distant metastasis in Ewing sarcoma: a multistate model

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Abstract

Background: We investigated the effects of surgical margins, histological response, and radiotherapy on local recurrence (LR), distant metastasis (DM), and survival in Ewing sarcoma.

Procedure: Disease evolution was retrospectively studied in 982 patients with Ewing sarcoma undergoing surgery after chemotherapy using a multistate model with initial state surgery, intermediate states LR, pulmonary metastasis (DMpulm), other DM ± LR (DMother), and final state death. Effect of risk factors was estimated using Cox proportional hazard models.

Results: The median follow-up was 7.6 years (95% CI, 7.2-8.0). Risk factors for LR are pelvic location, HR 2.04 (1.10-3.80), marginal/intralesional resection, HR 2.28 (1.25-4.16), and radiotherapy, HR 0.52 (0.28-0.95); for DMpulm the risk factors are <90% necrosis, HR 2.13 (1.13-4.00), and previous pulmonary metastasis, HR 4.90 (2.28-8.52); for DMother are 90% to 99% necrosis, HR 1.56 (1.09-2.23), <90% necrosis, HR 2.66 (1.87-3.79), previous bone/other metastasis, HR 3.08 (2.03-4.70); and risk factors for death without LR/DM are pulmonary metastasis, HR 8.08 (4.01-16.29), bone/other metastasis, HR 10.23 (4.90-21.36), and <90% necrosis, HR 6.35 (3.18-12.69). Early LR (0-24 months) negatively influences survival, HR 3.79 (1.34-10.76). Once DMpulm/DMother arise only previous bone/other metastasis remain prognostic for death, HR 1.74 (1.10-2.75).

Conclusion: Disease extent and histological response are risk factors for progression to DM or death. Tumor site and surgical margins are risk factors for LR. If disease progression occurs, previous risk factors lose their relevance. In case of isolated LR, time to recurrence is important for decision-making. Radiotherapy seems protective

for LR especially in pelvic/axial. Low percentages of LR in extremity tumors and associated toxicity question the need for radiotherapy in extremity Ewing sarcoma.

§8.1 Introduction

Ewing sarcoma is an aggressive primary bone tumor, predominantly affecting children and young adults.[61] At the time of diagnosis, 20% to 25% of the patients present with pulmonary (70-80%) and/or osseous (40-50%) metastases. A multimodal approach to treatment drastically improved survival of patients with localized Ewing sarcoma, with a 10-year overall survival (OS) of 55% to 65% nowadays. However, local recurrence, distant metastasis, and poor survival in patients with metastatic disease with a 5-year OS of 20% to 35% still remain of great concern.[95, 68] One of the strongest risk factors is the presence of metastasis at diagnosis[96, 52] and site of metastatic lesions; patients with extrapulmonary metastasis do significantly worse than patients with pulmonary metastasis alone.[95, 43] Other well-known risk factors are the primary tumor site[11, 30, 84] and tumor volume and/or size.[43, 25, 67, 63] Principles of treatment consist of neoadjuvant chemotherapy followed by local treatment of the primary tumor, either by surgery, radiotherapy, or both, and adjuvant chemotherapy. The histological response, assessed after surgery, is a strong additional prognostic factor for OS.[11, 25, 67] The effect of surgical margins on survival is controversial. The risk of local relapse is significantly lower after wide resection compared with marginal or intralesional resections.[113, 26] How the occurrence of a local recurrence may affect OS is not yet clearly established.[84, 22] If surgery with or without radiotherapy is superior compared with radiotherapy only in order to maximize local control alone is also under debate. Existing evidence is based on retrospective, nonrandomized trials.[134, 136] Several studies show advantage of postoperative radiotherapy (PORT) for patients with marginal or intralesional resections in terms of improved local control and event-free survival.[25, 63, 113, 134, 160] Possible associations between PORT and overall survival, and between local recurrence and OS, are not yet clearly established. The main problem in current studies on prognostic factors for Ewing sarcoma is that they are hampered by the choice of outcome variable. In general, overall survival, local recurrence-free survival, and disease-free survival are reported. Multiple analyses for these different endpoints are usually utilized; however, the relationship between those different endpoints cannot be investigated by using separate models. Multistate models can overcome these problems since the evolution of the disease and the occurrence of intermediate events, such as local recurrence and distant metastasis, which occur after surgery, are incorporated in the model, which provides useful insights into their relation with the considered endpoint, usually death.[12, 119, 21]

This study aims to investigate the effect of surgical margins, histological response, and radiotherapy, on local recurrence (LR), distant metastasis (DM), and OS in a large cohort of patients with Ewing sarcoma treated according to the EURO-E.W.I.N.G 99 protocol (EUROpean Ewing tumor Working Initiative of National Groups-Ewing Tumor Studies).

§8.2 Methods

This retrospective study was reviewed and approved by the institutional review board of the Leiden University Medical Center (Leiden, the Netherlands), and a waiver for informed consent was granted. A retrospective analysis of patients from the GPOH registry (Gesellschaft für Pädiatrische Onkologie und Hämatologie) treated in or according to the EURO-E.W.I.N.G 99 (EE99) protocol[8] was performed. All patients were treated between 1999 and 2009, and followed up until the end of 2017. All patients were treated according to the protocol with the aim to administer six cycles of VIDE (vincristine, ifosfamide, doxorubicin, etoposide) induction chemotherapy followed by local treatment of the primary tumor. The choice of local treatment, surgery with or without radiotherapy or definitive radiotherapy, was directed by specific guidelines in the protocol; however, the choice of the local multidisciplinary team prevailed. According to the EE99, protocol surgery was favored whenever feasible; only in case of an inoperable lesion that cannot be completely resected or a tumor in a critical site where complete surgery would cause unacceptable morbidity, definitive radiotherapy is indicated. Preoperative radiotherapy was indicated in case of clinical progression under chemotherapy or anticipated marginal or intralesional respectability. PORT was indicated in intralesional or marginal surgery and advised in cases with a poor histological response (<90% necrosis) regardless of surgical margins. Advised radiotherapy doses were 44.8-54.4 Gy, with a boost to a maximum of 64 Gy using a shrinking field technique. After local treatment, patients received maintenance chemotherapy. Only patients who underwent surgery (with or without radiotherapy) of the primary tumor after induction chemotherapy were eligible for inclusion in this study. A total of 982 patients, 470 study patients and 512 registry patients (who were treated according to the protocol but not randomized), were found to be eligible for inclusion in this study.

§8.2.1 Measures

The following data were extracted from the GPOH registry: age (0-10 years; 11-18 years; >18 years), gender, disease extent (localized, pulmonary metastasis only, other metastasis), tumor volume (<200 mL/≥ 200 mL), tumor location (extremity/axial nonpelvic/pelvic), PORT (yes/no), surgical margin (wide/marginal/intralesional), histological response (<90%/90-99%/100% necrosis), and follow-up data on LR, distant metastasis pulmonary (DMpulm), distant metastasis extrapulmonary with or without pulmonary metastasis (DMother). Histological response and resection margins were assessed on the surgical specimen by experienced local pathologists. Local recurrence was defined as local regional recurrence after initial complete response. Distant metastasis was defined as new metastatic disease or recurrence of metastatic disease after initial complete response.

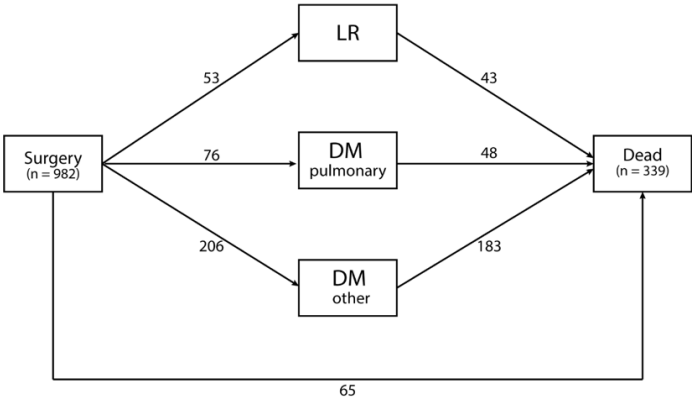

Figure 8.1: Multistate model for Ewing sarcoma

§8.2.2 Statistical analysis

OS was measured from the date of surgery, until the last day of follow-up, or date of death and evaluated using Kaplan-Meier estimates. To model disease progression, the multistate model illustrated in Figure 8.1 was estimated. The following five states are considered: alive after surgery without adverse events (state 1, surgery); alive with LR (state 2, LR); alive with pulmonary DM (state 3, DMpulm); alive with other DM (state 4, DMother); death (state 5). The effect of risk factors on each specific transition was estimated by using a Cox proportional hazard regression model; hazard ratios (HRs) along with their 95% confidence intervals (95% CI) were estimated.

§8.2.3 Missing data

For 776 (79%) of the 982 patients, information on all the covariates of interest was complete. Missing data were observed for the variable histological response (19%) and surgical margins (5%). In order to make full use of the available data, missing values were imputed using multiple imputation. Five complete data sets were generated. The multistate model was estimated on each of the imputed data sets, and the results were then combined using the Rubin rule.[126] Multiple imputation is a well-known technique used to reconstruct data when there is a small percentage of missing data. Another common approach is to drop cases with missing values and only analyze complete cases; however, this reduces the number of patients and therefore the power of the statistical tests and may even lead to biased results in some scenarios.[138]

All analyses were performed using R version 3.5.1.[122] The R-package mstate[49] was used to estimate the multistate model and to compute the occupation probabilities. The R-package Amelia II was used to impute the missing data.[82]

§8.3 Results

Table 8.1 summarizes patient and tumor characteristics and treatment for the 982 included patients, 470 study and 512 registry patients, at the time of surgery. The median follow-up, estimated with reversed Kaplan-Meier analysis, was 7.6 years (95% CI, 7.2-8.0 years). The 5-year OS was 74% (71-77%) for localized disease, 56% (47-55%) for pulmonary metastasis, and 43% (33-53%) for extrapulmonary metastasis. For patients who only had surgery as local treatment, 5-year OS was 75% (71-79%) for localized disease, 52% (39-65%) for pulmonary metastasis, and 41% (28-54%) for extrapulmonary metastasis. For patients who had surgery with radiotherapy, the 5-year OS was 74% (69-79%) for localized disease, 59% (47-71%) for pulmonary metastasis only, and 48% (31-65%) for extrapulmonary metastasis. In the group of patients treated with surgery and radiotherapy, there were more pelvic tumors (21% vs 15% in the surgery group), more marginal and intralesional surgical margins (39% vs 21% in the surgery group), and fewer patients with 100% tumor necrosis (33% vs 52% in the surgery group). The other patient and tumor characteristics were similar between both groups; see also Appendix 8.A.

In total, 53 patients of 982 (5%) developed isolated LR, 8% (14 of 169) of pelvic tumors, 8% (30 of 388) of nonpelvic axial tumors, and 2% (9 of 425) of extremity tumors. The percentage of LR was similar for patients treated with surgery and surgery with radiotherapy, 6% versus 5%, respectively. Seventy-six (7%) of the patients moved from surgery to DMpulm, and 28 (of 128) patients with isolated pulmonary metastasis at diagnosis developed new pulmonary metastasis during follow-up. The percentage of patients who developed new pulmonary metastasis was similar for patients treated with surgery and surgery with radiotherapy, 7% versus 8%, respectively. Two hundred six (21%) of the patients moved from surgery to DMother, and 39% (33 of 84) patients with previous bone/other metastasis and 21% (27 of 128) of patients with pulmonary metastasis only developed new extrapulmonary metastasis during follow-up. The percentage of patients who developed new extrapulmonary metastasis was similar for patients treated with surgery and surgery with radiotherapy, 20% versus 22%, respectively. Table 8.2 provides more details of the patient and tumor characteristics of patients who developed local recurrence, pulmonary metastasis, and other/bone metastasis with or without local recurrence with respect to the local treatment modality used. Sixty-five (7%) of the patients died without the occurrence of LR or DM. Sixty percent (39/65) of these patients had metastatic disease at diagnosis and died of progressive disease. Nine percent (6/65) died of therapy-related complications, and 15% (10/65) due to a secondary malignancy. For the remaining 10 patients, the cause of death was unknown. In total, 339 patients (35%) died.

HRs for each risk factor along with their 95% CI for each transition are reported in Table 8.3. The main prognostic factors for moving from surgery to LR are primary tumors located in the pelvis (HR 2.04; 95% CI, 1.10-3.80) and marginal or intralesional resection margins (HR 2.28; 95% CI, 1.25-4.16). The administration of radiotherapy seems protective for LR for all tumor sites combined (HR 0.52; 95% CI, 0.28-0.95). Radiotherapy was not randomized in this study, but was recommended, in the EE99 protocol, in case of intralesional or marginal resection and in case of poor histological

Table 8.1: Patient demographics and treatment characteristics after surgery for the 982 included patients

Characteristic	n (%)	Study n (%)	Registry n (%)
Total	982	470	512
Gender			
Male	590 (60)	280 (60)	310 (60)
Female	392 (40)	190 (40)	202 (40)
Age			
0-10 years	252 (26)	117 (25)	135 (26)
11-18 years	452 (46)	225 (48)	227 (44)
>18 years	278 (28)	128 (27)	150 (30)
Primary tumor localization			
Pelvic	169 (17)	75 (16)	94 (18)
Non-pelvic	813 (83)	395 (84)	418 (82)
Extremity	425 (43)	224 (48)	201 (40)
Axial	388 (40)	171 (36)	217 (42)
Volume at diagnosis			
<200 ml	577 (59)	311 (66)	266 (52)
≥200 ml	405 (41)	159 (34)	246 (48)
Disease extent at diagnosis			
Localized	770 (78)	417 (89)	353 (69)
Pulmonary metastasis	128 (13)	53 (11)	75 (15)
Extrapulmonary metastasis	84 (9)	0 (0)	84 (16)
Surgical margin			
Wide	717 (73)	352 (75)	365 (71)
Marginal	161 (16)	74 (16)	87 (17)
Intralesional	104 (11)	44 (9)	60 (12)
Histological response			
100%	426 (43)	225 (48)	202 (39)
90-99%	284 (29)	151 (32)	133 (26)
<90%	271 (28)	94 (20)	177 (35)
Post-operative radiotherapy			
No	550 (56)	284 (60)	266 (52)
Yes	432 (44)	186 (40)	246 (48)

Table 8.2: Patient, tumor, and treatment characteristics of patients who developed local recurrence, pulmonary metastasis, and other/bone metastasis with or without local recurrence

Characteristic	Total, n (%)	Surgery (n = 550)	Surgery + radiotherapy (n = 432)
Local recurrence	53/982 (5)	33 (6)	20 (5)
Location primary tumor			
Extremity	9/425 (2)	7	2
Non-pelvic axial	30/388 (8)	16	14
Pelvic	14/169 (8)	10	2
Surgical margin			
Wide	30/717 (4)	23	7
Marginal	12/161 (7)	4	8
Intralesional	11/104 (11)	6	5
Histological response			
100%	16/426 (4)	13	3
90-99%	19/284 (7)	11	8
<90%	18/271 (7)	9	9
Distant metastasis - pulmonary	76/982 (8)	41 (7)	35 (8)
Disease extent			
Localized	46/770 (6)	24	22
pulmonary metastasis	28/128 (22)	15	13
Bone/other metastasis	2/84 (2)	2	0
Histological response			
100%	25/426 (6)	18	7
90-99%	26/284 (9)	15	11
<90%	25/271 (9)	8	17
Distant metastasis - bone/other with or without LR	206 (21)	110 (20)	96 (22)
Disease extent			
Localized	146/770 (19)	76	70
Metastatic pulmonary	27/128 (21)	11	16
Metastatic bone/other	33/84 (39)	23	10
Histological response			
100%	65/426 (15)	37	28
90-99%	60/284 (21)	35	25
<90%	81/271 (30)	38	43

response (<90% necrosis) regardless of surgical margins. Guidelines were not always followed: 143 patients (97/266 [36%] registry and 46/284 [16%] study patients) treated with surgery alone had, based on the protocol guidelines, an indication for PORT and 190 patients (106/246 [43%] registry and 84/186 [45%] study patients) who received PORT had no indication for it based on the protocol guidelines. The main prognostic factor for patients moving from surgery to new pulmonary metastasis is a histological response of less than 90% necrosis (HR 2.13; 95% CI, 1.13- 4.00) and previous pulmonary metastasis (HR 4.90; 95% CI, 2.28-8.52). Risk factors for the transition surgery to new bone/other DM with or without LR are histological response (HR 1.56; 95% CI, 1.09-2.23 for 90-99% necrosis and HR 2.66; 95% CI, 1.87-3.79 for <90% necrosis) and previous bone/other metastasis with or without pulmonary metastasis (HR 3.08; 95% CI, 2.03-4.70). Disease extent (HR 8.08; 95% CI, 4.01-16.29 for pulmonary metastasis and HR 10.23; 95% CI, 4.90- 21.36 for bone/other metastasis) and histological response (HR 6.35; 95% CI, 3.18-12.69 for <90% necrosis) are risk factors for transition surgery to death. The administration of radiotherapy, which is not given randomly, seems to be protective (HR 0.45; 95% CI, 0.26-0.76). The effect of time to recurrence is prognostic for survival with an HR of 3.79 (95% CI, 1.34-10.76) for recurrence in the first 0 to 24 months. Histological response and disease extent are risk factors for DMpulm, but in the presence of new pulmonary disease, no statistically significant effect of histological response and disease extent on survival was observed. Histological response was also a risk factor for transition surgery to DMother, but in the presence of new metastatic disease, only previous bone/other metastasis with or without pulmonary metastasis remains of prognostic value in the presence of new metastatic disease (HR 1.74; 95% CI, 1.10-2.75).

The estimated multistate model was used to estimate outcome probabilities for specific patients Figure 8.1 visualizes the effect of local treatment modality on the patient-specific state occupation probabilities at different time points after surgery. The distance between two curves represents the probability of being in a specific state at a specific time point. After surgery, the probability of occupying the state "local treatment" decreases. The probabilities of occupying the states "local recurrence", "DMpulm", and "DMother" are similar for patients treated with surgery and surgery with radiotherapy regardless of the tumor site, surgical margins and histological response. However, radiotherapy was not randomized, so these results should be interpreted with caution.

Table 8.3: HRs and 95% CIs for all prognostic factors and the different transitions in the multistate model

	1: Surgery →LR		2: Surgery →DMpulm		3: Surgery →DM other		4: Surgery →death		5: LR →death		6: DMpulm →death		7: DMother →death	
Predictor	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Age														
0-10 years					1								1	
11 - 18 years					1.55	1.05 - 2.27							0.85	0.56 - 1.31
>18 years					1.85	1.24 - 2.76							0.97	0.60 - 1.55
Tumor site														
Non-pelvic	1		1		1								1	
Pelvic	2.04	1.10 - 3.80	1.64	0.96 - 2.83	1.32	0.93 - 1.86							0.98	0.66 - 1.44
Disease extent														
Localized + <200ml			1		1		1				1		1	
Localized + ≥200 ml			1.47	0.82 - 2.62	1.34	0.96 - 1.86	1.87	0.91 - 3.85			1.34	0.62 - 2.88	1.06	0.73 - 1.53
Metastatic pulmonary			4.90	2.82 - 8.52	1.52	0.98 - 2.36	8.08	4.01 - 16.29			0.77	0.38 - 1.57	0.96	0.59 - 1.56
Metastatic other			0.62	0.15 - 2.62	3.08	2.03 - 4.70	10.23	4.90 - 21.36			1.38	0.16 - 11.67	1.74	1.10 - 2.75
Surgical margin														
Wide	1				1								1	
Marginal / intralesional	2.28	1.25 - 4.16			0.79	0.57 - 1.10							1.31	0.92 - 1.87
Histological response														
100%	1		1		1		1		1		1		1	
90-99%	1.43	0.73 - 2.79	1.49	0.84 - 2.63	1.56	1.09 - 2.23	1.17	0.50 - 2.74	1.02	0.37 - 2.81	1.79	0.82 - 3.92	0.91	0.60 - 1.38
<90%	1.13	0.48 - 2.66	2.13	1.13 - 4.00	2.66	1.87 - 3.79	6.35	3.18 - 12.69	0.86	0.18 - 4.14	1.32	0.60 - 2.92	1.14	0.77 - 1.69
Radiotherapy														
No	1		1		1		1		1				1	
Yes	0.52	0.28 - 0.95	0.82	0.51 - 1.31	0.99	0.73 - 1.32	0.45	0.26 - 0.76	1.53	0.65 - 3.64			1.08	0.78 - 1.49
Time to recurrence														
>24 months									1				1	
0-24 months									3.79	1.34 - 10.76			1.06	0.65 - 1.73

Abbreviations: DMpulm, distant metastasis solitary pulmonary; DMother, distant metastasis extrapulmonary with or without pulmonary metastasis; HR, hazard ratio; 95%CI, 95% confidence interval; LR, local recurrence

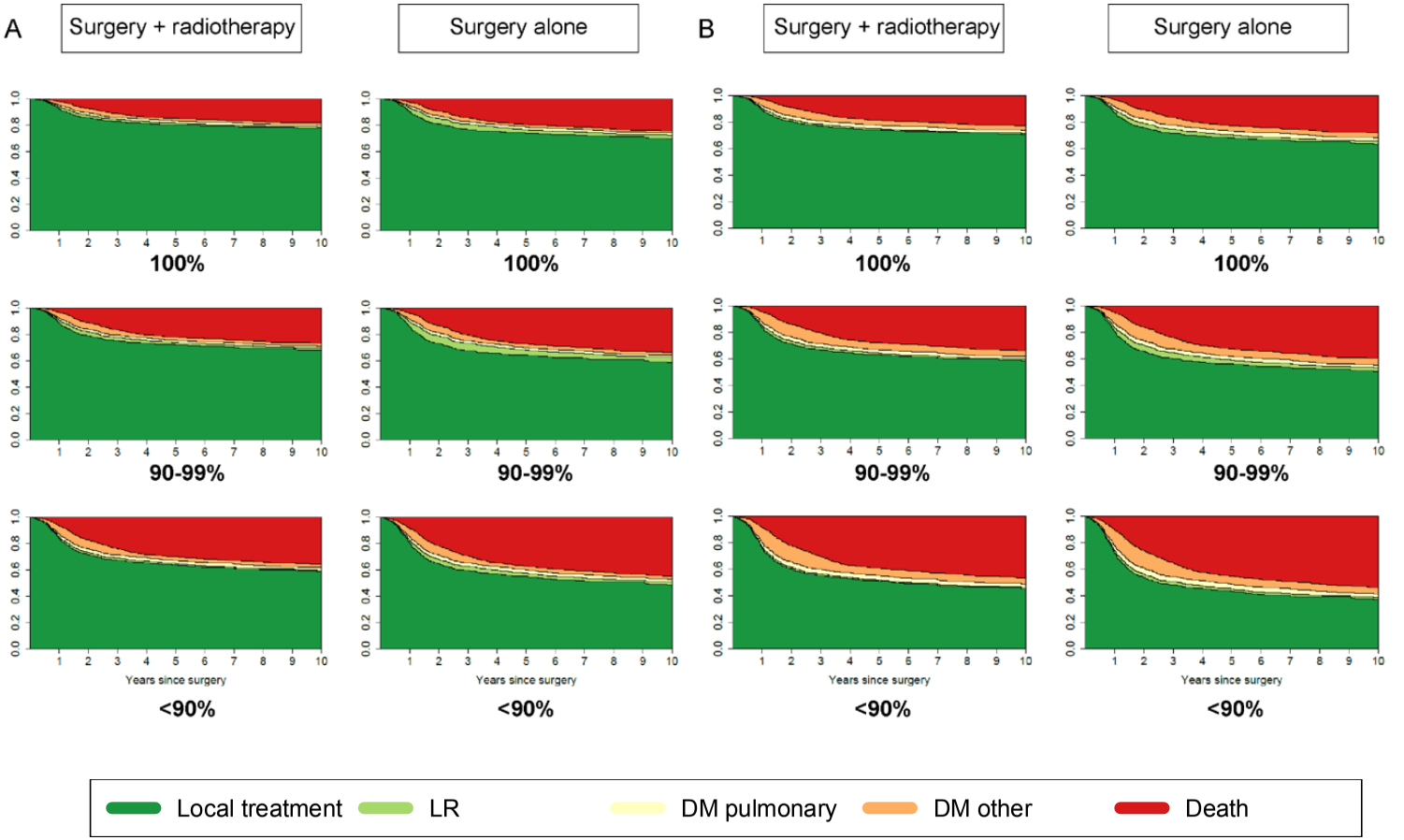

Figure 8.1: State occupation probabilities for patients with different local treatment strategies. Estimations are based on the model presented in Figure 1 and Table 2 and shows state occupation probabilities for (A) patient 1: aged 10-18 with a localized nonpelvic Ewing sarcoma and marginal or intralesional resection margins who is treated with surgery + radiotherapy (left panel) or surgery alone (right panel) for 100% necrosis, 90-99% necrosis, and <90% necrosis. (B) Patient 2: aged 10-18 with a localized pelvic Ewing sarcoma and wide resection margins who is treated with surgery + radiotherapy (left panel) or surgery alone (right panel) for 100% necrosis, 90-99% necrosis, and <90% necrosis

§8.4 Discussion

In Ewing sarcoma, local recurrence, distant metastasis, and poor survival in patients with metastatic disease remain of great concern. Associations between local treatment modality, local recurrence, distant metastasis, and death are not yet clearly established. In this study, we investigated the effect of surgical margins, histological response, and radiotherapy on the intermediate events local recurrence, distant metastasis, and on survival in a large cohort of patients with Ewing sarcoma using a multistate model.

Marginal or intralesional surgical margins are an important risk factor for transition from surgery to LR, and when a patient reaches the LR state, it was observed that the probability of death is higher in case of early LR (0-24 months), so time to recurrence could be considered as most relevant in these situations. Histological response is a strong prognostic factor for transition from surgery to distant metastasis and death. When a patient experiences new distant metastasis (either pulmonary, bone, other, or combined), histological response loses relevance as a risk factor as the occurrence of distant metastasis more dramatically affects survival. Administration of radiotherapy seems to be protective for LR. Other prognostic factors identified in this study were the primary tumor site and disease extent. A pelvic tumor site is an important risk factor for transition from surgery to LR. Previous pulmonary metastasis is a risk factor for transition to new pulmonary disease, but when a patient experiences new pulmonary disease, previous pulmonary metastasis is no longer prognostic factor for survival. Previous pulmonary or bone/other metastasis is a risk factor for transition to new bone/other metastasis with or without simultaneous LR. When reaching the DMother state only previous bone/other metastasis remains of prognostic value for survival.

The prognostic value of disease extent,[95, 96, 52, 43] histological response,[11, 25] primary tumor site,[11, 30, 84] and surgical margins[25, 113, 26, 22] observed in this study is consistent with previous studies. Several large studies show an advantage of PORT for patients with marginal or intralesional resections.[25, 63, 113, 134, 160] In addition to previous studies, this study has extended the knowledge about the effect of prognostic factors for intermediate events and final event death in Ewing sarcoma. We showed that prognostic factors have different effects on different transitions and that the impact on the next state in the evolution of the disease depends on the state a patient occupies. Apart from the patient's history, the time element is also of paramount importance for decision-making. LR within 2 years or the occurrence of distant metastasis with or without subsequent LR significantly affects survival chances, and despite our efforts as physicians almost all patients who experience such an event died of progressive disease. Therefore, the balance between the toxicity of intensive salvage treatments and quality of life in the remaining life span of these patients should be carefully considered. In case of late local recurrence (at least 2 years after treatment) there is no standard approach. The patients' age and preferences, previous treatment and tumor characteristics such as location, should all be considered and discussed in a multidisciplinary setting.

Radiotherapy seems protective for LR in all tumor sites combined, even in case

of good histological response. However, radiotherapy is not given randomly and is strongly correlated to patient and tumor characteristics; therefore, a note of caution in the interpretation of the results is required here. Patients treated with PORT generally have more tumor located in the pelvic, more inadequate surgical margins, and poorer histological response, which could have biased the results (see also Appendix 8.A). The incidence of local recurrence, especially in extremity Ewing sarcoma, is low. Only 2% (9 of 425) of the patients with extremity tumors developed isolated LR versus 8% (14 of 169) of the pelvic tumors and 8% (30 of 388) of the non-pelvic axial tumors. The number needed to treat (NNT) with surgery and radiotherapy to prevent the occurrence of a single LR is 72 for all tumor sites combined. In contrast, the NNT for extremity tumors is 80 and the NNT for pelvic tumors is 10. Which questions the value of radiotherapy in patients with an extremity Ewing sarcoma, where an individual patient with an extremity Ewing sarcoma might benefit, only few really are in need for this potentially toxic treatment, especially in the growing child. Radiotherapy is associated with a significant risk for secondary radiotherapy-induced malignancies, growth disturbance and postoperative complications of surgical reconstructions.[70] In case of Ewing sarcoma in a high-risk location, such as the pelvic or axial skeleton, this study showed that the administration of radiotherapy seems protective for LR, proton beam therapy could, in theory, be the solution in these cases; however, long-term data on radiation-induced late effects of proton beam radiation are not available yet. Prevention of distant metastasis and local recurrence appears to be the key to improve outcome in Ewing sarcoma, but distant metastases are still the main cause of treatment failure, and the results suggest that the use of radiotherapy is not protective for the occurrence of distant metastasis.

We compared the results presented in this article, which were computed using multiple imputation for missing data, to 776 complete cases and found that HRs were of similar magnitude. More details can be found in Appendix 8.B. We used a large cohort of patients with Ewing sarcoma, which strengthens this study. However, several limitations exist. Some subgroups are small; therefore, we cannot ensure that our findings of no effect of certain risk factors are not a result of the low number of events in these subgroups. Secondly, histological response and surgical margins were assessed by the local pathologist. The design of the study, in which a retrospective analysis was performed using a prospectively collected cohort, made revision of surgical margins and histological response not possible. Clear definitions were stated in the protocol, but differences in interpretation and evaluation could still exist. Third, cohorts often contain more variables than can reasonably be used for prediction, and for sufficient power one needs at least 10 events per variable. We therefore choose to select the most predictive and sensible predictors to be included in the analysis. Using a more extensive variable profile would have led to reduced predictability. Lastly, the recommendations for the use of radiotherapy were not consistently followed, and the results from this study are subjected to confounding by indication. Therefore, caution is needed when interpreting these results. Since the cohort used in this study is large and treated according to one protocol, we feel that the cohort adequately represents the population of interest and that the results are generalizable.

§8.5 Conclusion

Disease extent at diagnosis and histological response are the main risk factors for progression to distant metastasis or death after surgery. Tumor site and surgical margins are important risk factors for local recurrence. In case disease progression occurs, previous risk factors lose significance. Only time to recurrence is important for decision-making, since early LR (0-24 months) negatively influences survival. Both local recurrence and distant metastasis significantly affect survival, and despite our efforts as physicians, almost all patients who experience an event died of progressive disease. Therefore, the balance between the toxicity of intensive salvage treatments and quality of life in the remaining life span of these patients should be carefully considered in these cases. Radiotherapy seems protective for LR when all tumor sites are combined. However, a very low percentage of local recurrence in extremity tumors and the associated long-term toxicity with the use of radiotherapy questions the indication of radiotherapy in all extremity cases. Indications for radiotherapy should be explored further, preferably in a prospective randomized setting.

Appendix

§8.A Patient characteristics

Table 8.A.1

Characteristic	Surgery n (%)	Surgery + radiotherapy n (%)
Total	550	432
Gender		
Male	335 (61)	255 (59)
Female	215 (39)	177 (41)
Age		
0-10 years	149 (27)	103 (24)
11-18 years	235 (43)	217 (50)
>18 years	166 (30)	112 (26)
Primary tumor localization		
Pelvic	80 (15)	89 (21)
Non-pelvic	470 (85)	343 (79)
Extremity	272 (50)	153 (35)
Axial	198 (35)	190 (44)
Volume at diagnosis		
<200 ml	336 (61)	241 (56)
≥ 200 ml	214 (39)	191 (44)
Disease extent at diagnosis		
Localized	431 (78)	339 (79)
Pulmonary metastasis	62 (11)	66 (15)
Extrapulmonary metastasis	57 (10)	27 (6)
Surgical margin		
Wide	453 (82)	264 (61)
Marginal	58 (11)	105 (24)
Intralesional	39 (7)	65 (15)
Histological response		
100%	284 (52)	142 (33)
90-99%	165 (30)	119 (28)
<90%	100 (18)	171 (39)
Transition to state		
Local recurrence	33 (6)	20 (5)
DMpulm	41 (8)	36 (8)
Extrapulmonary metastasis	113 (21)	99 (23)
Alive without disease	359 (65)	284 (66)

§8.B Complete case analysis

Table 8.B.1: Hazard ratios and 95% confidence intervals for all prognostic factors and the different transitions in the multistate model only containing complete cases (n = 776)

	1: Surgery →LR		2: Surgery →DMpulm		3: Surgery →DM other		4: Surgery →death		5: LR →death		6: DMpulm →death		7: DMother →death	
Predictor	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Age														
0-10 years					1								1	
11-18 years					1.52	0.99 - 2.32							0.84	0.53 - 1.35
>18 years					1.76	1.12 - 2.79							1.15	0.55 - 1.58
Tumor site														
Non-pelvic	1		1		1								1	
Pelvic	2.56	1.23 - 5.33	1.50	0.83 - 2.72	1.53	1.06 - 2.20							0.99	0.66 - 1.49
Disease extent														
Localized + <200ml			1		1		1				1		1	
Localized + ≥200 ml			1.26	0.68 - 2.33	1.22	0.84 - 1.76	1.82	0.81 - 4.06			1.34	0.60 - 3.00	0.96	0.64 - 1.45
Metastatic pulmonary			3.91	2.14 - 7.11	1.50	0.93 - 2.42	8.94	4.10 - 19.46			0.76	0.35 - 1.63	0.91	0.53 - 1.55
Metastatic other			0.67	0.16 - 2.86	3.22	2.03 - 5.11	10.82	4.70 - 24.94			1.35	0.16 - 11.73	1.63	0.98 - 2.71
Surgical margin														
Wide	1				1								1	
Marginal / intralesional	2.40	1.07 - 5.39			0.88	0.58 - 1.32							1.30	0.84 - 2.01
Histological response														
100%	1		1		1		1		1		1		1	
90-99%	1.50	0.71 - 3.16	1.62	0.90 - 2.91	1.64	1.12 - 2.42	1.27	0.55 - 2.94	1.00	0.40 - 2.50	1.97	0.89 - 4.36	0.90	0.58 - 1.39
<90%	1.08	0.42 - 2.79	2.25	1.21 - 4.17	2.81	1.91 - 4.12	8.32	4.16 - 16.64	0.57	0.15 - 2.22	1.32	0.57 - 3.06	1.15	0.76 - 1.73
Radiotherapy														
No	1		1		1		1		1				1	
Yes	0.51	0.24 - 1.09	0.96	0.58 - 1.61	1.04	0.75 - 1.45	0.54	0.30 - 0.96	1.87	0.62 - 5.61			1.00	0.70 - 1.43
Time to recurrence														
>24 months									1				1	
0-24 months									5.76	1.65 - 20.17			1.05	0.61 - 1.79

Abbreviations: DMpulm, distant metastasis solitary pulmonary; DMother, distant metastasis extrapulmonary with or without pulmonary metastasis; HR, hazard ratio; 95%CI, 95% confidence interval; LR, local recurrence