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Treatment Patterns and Outcomes in Adolescents and Adults Treated for Ewing Sarcoma: A Retrospective Single-Center Cohort Study

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Abstract

Background

Ewing sarcoma is a rare, aggressive small round cell sarcoma affecting mainly children, adolescents, and young adults. Evidence on treatment delivery, toxicity, and long-term outcomes in adults remains limited.

Methods

This retrospective single-center cohort study included patients aged ≥ 16 years treated at the National Cancer Institute, Bratislava, Slovakia, from January 2007 through June 2026 for Ewing sarcoma or selected historical round cell sarcoma diagnoses considered compatible with Ewing sarcoma. Response and toxicity were assessed using Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) and Common Terminology Criteria for Adverse Events version 5.0 (CTCAE 5.0). Overall survival (OS) and progression-free survival (PFS) were estimated using Kaplan–Meier methods; the association of metastatic disease at diagnosis with time-to-event outcomes was explored using univariable Cox proportional hazards models. Median follow-up was estimated using reverse Kaplan–Meier analysis.

Results

Among 41 patients, median age at diagnosis was 33.6 years (range, 16.7–68.5), and 25 (61.0%) had metastatic disease at diagnosis. A characteristic Ewing sarcoma-associated gene fusion was molecularly confirmed in 19 patients (46.3%). The objective response rate (ORR) was 82.9% (34/41) overall and 85.2% (23/27) among patients who had received neither surgery nor radiotherapy before induction chemotherapy. Median follow-up was 63.7 months (95% confidence interval [CI], 47.7–104.5). Median OS and PFS were 70.3 and 26.4 months, respectively. Metastatic disease was associated with shorter PFS (median, 13.2 vs 75.1 months; hazard ratio [HR], 2.50; 95% CI, 1.02–6.12; Cox model P = .045; log-rank P = .036). OS was numerically shorter in metastatic disease (median, 21.8 months vs not reached; HR, 2.15; 95% CI, 0.81–5.74; Cox model P = .126; log-rank P = .117). Grade 4 neutropenia occurred in 30/41 patients (73.2%), febrile neutropenia in 20/41 (48.8%), and dose reductions were recorded in 25/41 (61.0%). No treatment-related deaths were recorded.

Conclusions

In this retrospective referral cohort, metastatic disease at diagnosis was associated with significantly shorter PFS, whereas the association with OS was imprecisely estimated and not statistically significant. High response rates coexisted with substantial hematologic toxicity and frequent dose reductions.

Interpretation is limited by the small sample size, treatment heterogeneity, and incomplete molecular confirmation.

Background

Ewing sarcoma is a rare, aggressive small round cell sarcoma arising in bone or soft tissue, with a peak incidence in the second decade of life. Although it can occur at any age, adults represent a minority of patients, and evidence regarding treatment delivery and outcomes in this population remains limited (1–4).

Ewing sarcoma is characterized by a fusion between a FUS/EWS/TAF15 (FET)-family gene, usually EWSR1 and rarely FUS, and an E26 transformation-specific (ETS)-family transcription factor. The most common fusion is EWSR1::FLI1, resulting from t(11;22)(q24;q12). Less common ETS partners include ERG, FEV, ETV1, and ETV4. Contemporary World Health Organization classification distinguishes Ewing sarcoma from other undifferentiated round cell sarcomas, including CIC-rearranged sarcoma, sarcoma with BCOR genetic alterations, and round cell sarcoma with EWSR1 non-ETS fusions. This distinction is particularly relevant when interpreting historical cohorts without comprehensive molecular testing (2, 3, 5, 6).

Treatment is multimodal and combines intensive systemic chemotherapy with definitive local control by surgery, radiotherapy, or both. Interval-compressed vincristine, doxorubicin, and cyclophosphamide alternating with ifosfamide and etoposide (VDC/IE) is a contemporary first-line standard. The EE2012 trial demonstrated more favorable outcomes with VDC/IE than with a European strategy based on vincristine, ifosfamide, doxorubicin, and etoposide (VIDE); the benefit of interval compression had previously been established in AEWS0031 (7–9, 13).

Despite therapeutic advances, outcomes remain poor for metastatic and recurrent disease. Disease extent at diagnosis is among the most important prognostic factors, together with tumor size and site and histopathologic response to chemotherapy (1, 14). Because Ewing sarcoma is uncommon in adults, much of the available evidence is derived from pediatric, adolescent, and young adult trials or retrospective adult series.

This retrospective study aimed to describe systemic and local treatment patterns, response to induction chemotherapy, hematologic toxicity, treatment at first recurrence, and long-term outcomes in adolescents and adults treated for Ewing sarcoma at a national sarcoma referral center. Associations between disease extent at diagnosis and survival were examined as exploratory analyses.

Methods

Study Design and Population

This retrospective single-center cohort study included patients treated at the National Cancer Institute, Bratislava, Slovakia, from January 2007 through June 2026. Eligibility criteria were age ≥ 16 years; a clinicopathologic diagnosis within the Ewing sarcoma spectrum, including selected historical round cell sarcoma diagnoses considered compatible with Ewing sarcoma; receipt of systemic anticancer therapy; and medical records sufficient for evaluation of treatment and time-to-event outcomes.

Historical diagnoses of peripheral primitive neuroectodermal tumor and selected undifferentiated small round cell sarcomas were included when the original pathologic, immunohistochemical, and clinical findings were considered compatible with Ewing sarcoma. For the exploratory subgroup analysis, cases were classified by skeletal versus extraskeletal origin and localized versus metastatic disease at diagnosis after review of individual records.

Forty-six potentially eligible patients were identified. Five were excluded because incomplete documentation or absence of subsequent oncology follow-up precluded reliable ascertainment of treatment outcomes and/or time-to-event endpoints. The final analytic cohort comprised 41 patients. The patient selection process is shown in Fig. 1.

[Insert Fig. 1 *here]*

Data Sources and Variables

Clinical, pathologic, molecular, treatment, response, toxicity, recurrence, and follow-up data were retrospectively abstracted from existing medical records. Disease extent at diagnosis was categorized as localized or metastatic. Molecular-genetic status was categorized as molecularly confirmed, testing negative, or testing not performed. Primary and metastatic sites were recorded as documented; patients could have more than one metastatic site. For the exploratory analysis, historical cases were classified as skeletal or extraskeletal and as localized or metastatic after individual record review.

Outcomes and Assessments

Radiologic response to induction chemotherapy was assessed according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) and categorized as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). Objective response rate (ORR) was defined as the proportion of patients with CR or PR. Patients without an evaluable radiologic response were retained in the denominator and counted as nonresponders in the overall cohort analysis. Response was also described separately in the 27 patients who received neither surgery nor radiotherapy before induction chemotherapy.

Overall survival (OS) was defined as the interval from initiation of first-line systemic therapy to death from any cause; patients alive at last follow-up were censored at the date of last known contact.

Progression-free survival (PFS) was defined as the interval from initiation of first-line therapy to the first documented progression or recurrence, or death from any cause, whichever occurred first.

Adverse events were graded according to Common Terminology Criteria for Adverse Events version 5.0 (CTCAE 5.0). Hematologic toxicity data were available for all 41 treated patients.

Bias, Study Size, and Missing Data

All potentially eligible patients identified during the study period were reviewed. Historical diagnoses were reassessed using available pathologic, immunohistochemical, and clinical information to reduce diagnostic misclassification. To limit distortion of radiologic response by prior local therapy, response was also reported in the subgroup that had received neither surgery nor radiotherapy before induction chemotherapy. No formal sample-size calculation was performed; all eligible patients with sufficiently complete records during the study period were included. Missing values were not imputed and are reported explicitly where applicable. Patients alive at last follow-up were censored at the date of last known contact.

Statistical Analysis

Categorical variables were summarized as counts and percentages, and age was summarized as median and range. OS and PFS were estimated using the Kaplan–Meier method and compared using two-sided log-rank tests. Associations between metastatic disease at diagnosis and time-to-event outcomes were explored using univariable Cox proportional hazards models, with hazard ratios (HRs) and 95% confidence intervals (CIs). The Breslow approximation was used for tied event times. Median follow-up was estimated using the reverse Kaplan–Meier method. Given the limited number of events (19 deaths and 25 PFS events), no multivariable Cox model was fitted. P values are two-sided and unadjusted for multiple testing; the prognostic analyses are exploratory. No formal sensitivity analyses were performed. Statistical analyses were performed using NCSS version 26.0.4 (NCSS, LLC, Kaysville, Utah, USA).

Reporting Guidance and Generative AI Assistance

Reporting was aligned with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations for cohort studies (31). During manuscript preparation, ChatGPT (OpenAI) was used for language editing, formatting assistance, and assistance with code generation for verification of descriptive and survival analyses. The investigators retained responsibility for the source data, analysis decisions, interpretation, and final manuscript.

Results

Patient Characteristics and Treatment

The final cohort comprised 41 patients; median age at diagnosis was 33.6 years (range, 16.7–68.5). There were 23 men (56.1%) and 18 women (43.9%). Sixteen patients (39.0%) had localized disease and 25 (61.0%) had metastatic disease. The pelvis was the most frequent primary site (14/41; 34.1%), followed by the lower extremity (10/41; 24.4%). A characteristic Ewing sarcoma-associated gene fusion was molecularly confirmed in 19 patients (46.3%). Among the remaining 22 patients (53.7%), molecular testing was negative in 11 (26.8%) and was not performed in 11 (26.8%). Baseline patient characteristics are summarized in Table 1.

[Insert Table 1 *here]*

Table 1
Baseline patient characteristics (N = 41)

Characteristic	Value
Age, median (range), years	33.6 (16.7–68.5)
Sex	
Male	23 (56.1)
Female	18 (43.9)
Disease extent at diagnosis	
Localized disease	16 (39.0)
Metastatic disease	25 (61.0)
Primary tumor site	
Upper extremity	4 (9.8)
Lower extremity	10 (24.4)
Chest	5 (12.2)
Abdomen	5 (12.2)
Pelvis	14 (34.1)
Other	3 (7.3)
Metastatic site at diagnosis	
Lung	10 (24.4)
Bone	8 (19.5)
Lymph nodes	13 (31.7)
Liver	1 (2.4)
Central nervous system	1 (2.4)
Other metastatic site	4 (9.8)
Molecular-genetic status	
Molecularly confirmed Ewing sarcoma	19 (46.3)
Ewing sarcoma not molecularly confirmed	22 (53.7)
Molecular testing negative	11 (26.8)
Molecular testing not performed	11 (26.8)

Percentages use the entire cohort (N = 41) as the denominator unless otherwise specified. Patients could have more than one metastatic site; metastatic-site percentages therefore do not sum to 100%. Detailed estimates from the exploratory classification by skeletal versus extraskeletal origin and disease extent are provided in Supplementary Table S1 (Additional file 1).

All 41 patients received first-line induction chemotherapy. The vincristine, ifosfamide, and doxorubicin regimen (VID), which did not include etoposide, was administered to 25 patients (61.0%); high-dose cyclophosphamide, doxorubicin, and vincristine (HD-CAV) to 10 (24.4%); and VDC/IE to 6 (14.6%). The historical three-drug VID regimen reflects institutional practice during the earlier treatment era and is distinct from the four-drug VIDE regimen evaluated in European trials.

Local treatment was performed before induction chemotherapy in 14 patients (34.1%): surgery alone in 10 (24.4%), external-beam radiotherapy alone in 1 (2.4%), and both modalities in 3 (7.3%); 27 patients (65.9%) received no local treatment before chemotherapy. After induction chemotherapy, local treatment was performed in 29 patients (70.7%): surgery alone in 7 (17.1%), external-beam radiotherapy alone in 15 (36.6%), and both modalities in 7 (17.1%). Ten patients (24.4%) received no local treatment after induction chemotherapy, and local-treatment data were missing for 2 (4.9%). Eleven patients received local treatment at both time points.

Response to Induction Chemotherapy

Across the entire cohort, CR was recorded in 13 patients (31.7%), PR in 21 (51.2%), and SD in 4 (9.8%); response was not evaluable in 3 (7.3%). The ORR was 82.9% (34/41). Among the 27 patients who received neither surgery nor radiotherapy before induction chemotherapy, CR was recorded in 5 (18.5%), PR in 18 (66.7%), and SD in 2 (7.4%); 2 patients (7.4%) were not evaluable. With these 2 non-evaluable patients retained in the denominator, the ORR was 85.2% (23/27). Responses by regimen are presented descriptively in Table 2. Regimens were not statistically compared because of small subgroup sizes and differences in treatment era.

Table 2
Response to induction chemotherapy in patients without prior surgery or radiotherapy (n = 27)

Regimen	n	CR, n (%)	PR, n (%)	SD, n (%)	Not evaluable, n (%)
VID	12	4 (33.3)	5 (41.7)	1 (8.3)	2 (16.7)
HD-CAV	9	1 (11.1)	7 (77.8)	1 (11.1)	0
VDC/IE	6	0	6 (100.0)	0	0
Overall	27	5 (18.5)	18 (66.7)	2 (7.4)	2 (7.4)

CR, complete response; PR, partial response; SD, stable disease; VID, vincristine, ifosfamide, and doxorubicin; HD-CAV, high-dose cyclophosphamide, doxorubicin, and vincristine; VDC/IE, vincristine, doxorubicin, and cyclophosphamide alternating with ifosfamide and etoposide.

Survival

Median follow-up estimated by the reverse Kaplan–Meier method was 63.7 months (95% CI, 47.7–104.5; observed follow-up range, 1.6–228.9 months). Nineteen deaths and 25 PFS events were recorded.

Median OS was 70.3 months. Estimated 2-year OS was 60.2% (95% CI, 42.1%–74.2%) and 5-year OS was 53.7% (95% CI, 35.7%–68.7%). Median PFS was 26.4 months; estimated 2-year PFS was 51.0% (95% CI, 33.7%–65.9%) and 5-year PFS was 35.8% (95% CI, 19.4%–52.5%).

Median OS was not reached in patients with localized disease and was 21.8 months in those with metastatic disease. Metastatic disease was associated with a numerically higher hazard of death, although the estimate was imprecise (HR, 2.15; 95% CI, 0.81–5.74; Cox model P = .126; log-rank P = .117).

Median PFS was 75.1 months in localized disease and 13.2 months in metastatic disease. In the univariable analysis, metastatic disease was associated with a higher hazard of progression, recurrence, or death (HR, 2.50; 95% CI, 1.02–6.12; Cox model P = .045; log-rank P = .036). Survival estimates by disease extent are summarized in Table 3, with the corresponding Kaplan–Meier curves shown in Figs. 2 and 3.

[Insert Table 3 *here]*

Table 3
Kaplan–Meier survival estimates according to disease extent at diagnosis

Outcome	Entire cohort	Localized disease	Metastatic disease
Number of patients	41	16	25
Median OS, months	70.3	Not reached	21.8
2-year OS	60.2%	73.7%	50.0%
5-year OS	53.7%	65.5%	44.4%
Median PFS, months	26.4	75.1	13.2
2-year PFS	51.0%	67.7%	38.2%
5-year PFS	35.8%	56.4%	19.1%

OS, overall survival; PFS, progression-free survival.

[Insert Fig. 2 *here]*

[Insert Fig. 3 *here]*

Exploratory Four-Group Analysis

The exploratory analysis comprised skeletal localized (n = 9), skeletal metastatic (n = 11), extraskeletal localized (n = 7), and extraskeletal metastatic (n = 14) subgroups. Global log-rank P values were .151 for OS and .049 for PFS. The skeletal metastatic subgroup had the shortest observed median OS (15.4 months) and PFS (13.2 months). Small subgroup sizes, imprecise estimates, and multiple unadjusted comparisons preclude firm conclusions about differences between these groups. Detailed estimates are provided in Supplementary Table S1 (Additional file 1). The corresponding Kaplan–Meier curves are shown in Figs. 4 and 5.

[Insert Fig. 4 *here]*

[Insert Fig. 5 *here]*

Hematologic Toxicity

Dose reductions were recorded in 25/41 patients (61.0%). Grade 4 neutropenia occurred in 30/41 patients (73.2%), febrile neutropenia in 20/41 (48.8%), grade 3–4 thrombocytopenia in 20/41 (48.8%), and grade 3–4 anemia in 12/41 (29.3%). No grade 4 anemia or treatment-related deaths were recorded. Regimen-specific hematologic toxicity and dose reductions are summarized in Table 4.

[Insert Table 4 *here]*

Table 4
Hematologic toxicity and dose reductions during induction chemotherapy (N = 41)

Toxicity	**HD-CAV (n = 10)**	**VDC/IE (n = 6)**	**VID (n = 25)**	**Overall (N = 41)**
Dose reduction	10 (100.0)	4 (66.7)	11 (44.0)	25 (61.0)
Grade 4 neutropenia	9 (90.0)	6 (100.0)	15 (60.0)	30 (73.2)
Febrile neutropenia	6 (60.0)	5 (83.3)	9 (36.0)	20 (48.8)
Grade 3–4 thrombocytopenia	6 (60.0)	3 (50.0)	11 (44.0)	20 (48.8)
Grade 4 thrombocytopenia	6 (60.0)	0	6 (24.0)	12 (29.3)
Grade 3–4 anemia	5 (50.0)	3 (50.0)	4 (16.0)	12 (29.3)
Grade 4 anemia	0	0	0	0

Values are numbers of patients and percentages within each regimen. HD-CAV, high-dose cyclophosphamide, doxorubicin, and vincristine; VDC/IE, vincristine, doxorubicin, and cyclophosphamide alternating with ifosfamide and etoposide; VID, vincristine, ifosfamide, and doxorubicin; CTCAE, Common Terminology Criteria for Adverse Events. Toxicity was graded according to CTCAE 5.0. The grade 4 thrombocytopenia row is a subset of the grade 3–4 thrombocytopenia row.

Treatment at First Recurrence

Disease recurrence occurred in 23 patients (56.1%). At first recurrence, 16/23 patients received systemic therapy and 7/23 were managed with local treatment alone. The primary systemic regimens were high-dose ifosfamide in 7 patients (30.4%), etoposide plus cisplatin (EP) in 5 (21.7%), vincristine, dactinomycin, and ifosfamide (VAI) in 2 (8.7%), doxorubicin in 1 (4.3%), and capecitabine plus temozolomide (CapTem) in 1 (4.3%). Local treatment was incorporated into the management of first recurrence in 10/23 patients overall (43.5%), including 7 (30.4%) in whom it was the sole treatment modality. The mutually exclusive primary treatment categories therefore comprised 16 patients receiving systemic therapy and 7 receiving local treatment alone.

Discussion

This cohort describes treatment patterns and hematologic toxicity in a referral population of adolescents and adults treated for Ewing sarcoma. Adult retrospective series provide complementary information to cooperative trials, particularly regarding treatment delivery and outcomes in routine practice (15, 17, 18, 21, 29, 30).

The high prevalence of metastatic disease at diagnosis (61%) must be considered when interpreting these results. Comparisons with localized-disease cohorts or prospective trials must account for differences in baseline risk, eligibility, diagnostic confirmation, and treatment era. Baldini et al. included 11 patients with metastatic disease among 37 adults, whereas Ahmed et al. reported separate localized and metastatic adult cohorts (15, 17, 18).

The ORR was 82.9% overall and 85.2% among the 27 patients without prior surgery or radiotherapy. Analyzing this subgroup reduces the influence of prior local treatment on radiologic response assessment, although response estimates still depend on the presence of assessable baseline disease and the timing of imaging relative to subsequent local treatment. Radiologic response should also be distinguished from histopathologic response after resection (14).

Systemic treatment varied across the study period. Most patients received VID without etoposide, whereas only 6 received interval-compressed VDC/IE. The historical three-drug VID regimen is distinct from the four-drug VIDE strategy evaluated in European trials. Randomized evidence supports interval-compressed VDC/IE in contemporary practice (8, 9, 13), but this heterogeneous cohort cannot establish comparative effectiveness between regimens. Small subgroup sizes and differences in treatment era and follow-up further limit such comparisons.

Metastatic disease was associated with shorter PFS in the univariable analysis (HR, 2.50; 95% CI, 1.02–6.12). The OS estimate was less precise (HR, 2.15; 95% CI, 0.81–5.74), encompassing both little or no association and a substantially higher hazard of death. These unadjusted findings are consistent with the established prognostic importance of disease extent but do not establish an independent association in this cohort (14–17).

The exploratory four-group analysis suggested variation in outcomes by primary tissue of origin and metastatic status. However, the small groups, few patients remaining at risk late in follow-up, and absence of multiplicity adjustment limit interpretation. The nominal log-rank P value for PFS (.049) should not be interpreted as confirmatory evidence of distinct prognostic groups.

Local treatment remains a fundamental component of multimodal management. External-beam radiotherapy was the most frequent local modality after induction chemotherapy in this cohort. Selection of surgery, radiotherapy, or both should account for anatomy, resectability, expected morbidity, and response to systemic therapy. Contemporary guidance emphasizes multidisciplinary decision-making (7, 18, 26, 27).

Disease recurrence was recorded in 56.1% of the cohort. High-dose ifosfamide was the most frequently used systemic regimen at first recurrence. Prognosis after recurrence is influenced by its timing and extent (19). The randomized rEECur program provides comparative evidence for systemic therapy in recurrent or refractory Ewing sarcoma (22–25); the present series describes institutional treatment patterns and does not compare salvage regimens.

Hematologic toxicity was substantial, with grade 4 neutropenia in 73.2%, febrile neutropenia in 48.8%, and dose reductions in 61.0%. No treatment-related deaths were recorded, but the small cohort precludes reliable inference regarding rare fatal toxicities. Interpretation of tolerability also requires consideration of supportive care, cycle delays, and delivered dose intensity. These are particularly relevant issues when applying intensive regimens to adults (21, 26, 27, 30).

Limitations include the retrospective single-center design, small sample size, and heterogeneous treatment across a prolonged study period. Eligibility required systemic treatment and adequate records, which may limit generalizability; exclusion of 5 potentially eligible patients may also introduce selection bias. Only 19 of 41 cases had reported molecular confirmation. Historical diagnoses, negative molecular tests, and untested cases may represent different levels of diagnostic certainty, and misclassification under contemporary World Health Organization categories cannot be excluded. Response assessment is complicated by prior local treatment in 14 patients. Survival associations were unadjusted, and subgroup estimates, particularly during late follow-up, are imprecise. As a national referral-center cohort with evolving historical treatment practices, referral patterns and management may differ from those in other institutions or health-care systems.

The main contribution of this study is a descriptive account of treatment delivery, toxicity, and outcomes in an adult-enriched referral cohort. Better molecular characterization and harmonized prospective data collection would improve the comparability of future cohorts and support the development of treatment strategies for metastatic and recurrent disease (28).

A comparison of our cohort with selected published retrospective and prospective studies is provided in Table 5.

Table 5
Comparison of the present cohort with selected published studies

Study	Design and population	Systemic treatment	Key survival outcomes	Main relevance
Present study	Single-center retrospective cohort, Slovakia, 2007–2026; 41 patients; age ≥ 16 years; 61% metastatic	VID 61%; HD-CAV 24%; VDC/IE 15%	Median OS 70.3 months; 5-year OS 53.7%; median PFS 26.4 months; 5-year PFS 35.8%	Metastatic disease was associated with shorter progression-free survival (HR 2.50)
Baldini et al., 1999 (15)	Single-center retrospective study; 37 adults; 26 localized and 11 metastatic	Multiagent chemotherapy in 35/37 patients	5-year OS 37% in the entire cohort	Localized disease and osseous origin were favorable prognostic factors
Ahmed et al., 2013 (18)	Single-center retrospective study; 102 adults with localized Ewing sarcoma; median age 27.6 years	Multimodal treatment	5-year OS 60%; 5-year EFS 52%	Outcomes improved in the modern treatment era
Ahmed et al., 2014 (17)	Single-center retrospective study; 36 adults with metastatic Ewing sarcoma	Multimodal treatment	4-year OS 20%; 4-year EFS 11%	Very poor outcomes in metastatic disease
Pretz et al., 2017 (29)	Retrospective study; 67 adults with localized Ewing sarcoma	Multimodal treatment based on VDC/IE	5-year OS 79%; 5-year PFS 66%; 5-year LRFS 91%	Supports the feasibility of VDC/IE–based multimodality therapy in adults
Hajjaj et al., 2024 (30)	Multicenter retrospective cohort, British Columbia; 107 patients, including 66 adults and 41 children	Contemporary multimodal treatment	5-year OS 58% in adults vs 75% in children; 74% among adults with localized disease	Adults had inferior outcomes compared with children
Ducrot et al., 2026 (16)	Multicenter observational real-world study; 156 patients; 82 metastatic at diagnosis and 74 with metastatic relapse	Multiple systemic and locoregional strategies	Median OS 31.4 months for metastatic disease at diagnosis and 20.3 months for metastatic relapse	Contemporary real-world benchmark for metastatic disease
Brennan et al., 2022 (9)	International randomized phase III EE2012 trial; 640 patients aged 2–49 years	VDC/IE versus a VIDE-based strategy	3-year EFS 67% vs 61%; adjusted HR 0.71; OS HR 0.62	Contemporary first-line benchmark supporting interval-compressed treatment

Values are reported as published in the original studies. OS, overall survival; PFS, progression-free survival; EFS, event-free survival; LRFS, local relapse-free survival; HR, hazard ratio; VID, vincristine, ifosfamide, and doxorubicin; HD-CAV, high-dose cyclophosphamide, doxorubicin, and vincristine; VDC/IE, vincristine, doxorubicin, and cyclophosphamide alternating with ifosfamide and etoposide; VIDE, vincristine, ifosfamide, doxorubicin, and etoposide. Direct cross-study comparisons are limited by differences in patient populations, treatment era, and endpoint definitions.

Conclusions

In this retrospective single-center cohort of adolescents and adults treated for Ewing sarcoma, high response rates coexisted with substantial hematologic toxicity and frequent dose reductions. Metastatic disease was associated with shorter PFS in univariable analysis, whereas the association with OS was imprecisely estimated and not statistically significant. These findings should be interpreted in the context of heterogeneous treatment, incomplete molecular confirmation, and the small sample size.

Abbreviations

CapTem
capecitabine plus temozolomide
CI
confidence interval
CR
complete response
CTCAE
Common Terminology Criteria for Adverse Events
EFS
event-free survival
EP
etoposide plus cisplatin
ETS
E26 transformation-specific
FET
FUS/EWS/TAF15
HD-CAV
high-dose cyclophosphamide,doxorubicin,and vincristine
HR
hazard ratio
LRFS
local relapse-free survival
ORR
objective response rate

OS
overall survival
PD
progressive disease
PFS
progression-free survival
PR
partial response
RECIST
Response Evaluation Criteria in Solid Tumors
SD
stable disease
VAI
vincristine,dactinomycin,and ifosfamide
VDC/IE
vincristine,doxorubicin,and cyclophosphamide alternating with ifosfamide and etoposide
VID
vincristine,ifosfamide,and doxorubicin
VIDE
vincristine,ifosfamide,doxorubicin,and etoposide.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee of the National Cancer Institute, Bratislava, Slovakia (reference number RS/Minarik/2026; approval dated 2 October 2026). The study was conducted in accordance with the Declaration of Helsinki. The approved protocol included a waiver of individual informed consent for this retrospective analysis of existing medical records using an anonymized analytical database.

Consent for publication

Not applicable.

Competing interests

Matúš Studený is an employee of Boehringer Ingelheim. Boehringer Ingelheim had no role in the design, conduct, analysis, interpretation, or reporting of this study. All other authors declare that they have no competing interests.

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Author Contribution

T.M. conceived the study and supervised the project. T.M, A.J, M.K, M.So., J.S., P.H., M.St. and M.M contributed to data aquisition. P.H. interpreted the results and drafted the manuscript. M.M. critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript

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Not applicable.

Data Availability

The datasets generated and/or analysed during the current study are not publicly available because they contain sensitive clinical information and are subject to institutional and ethical restrictions. Anonymized data may be available from the corresponding author upon reasonable request and subject to approval by the National Cancer Institute, Bratislava, Slovakia.

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Figures

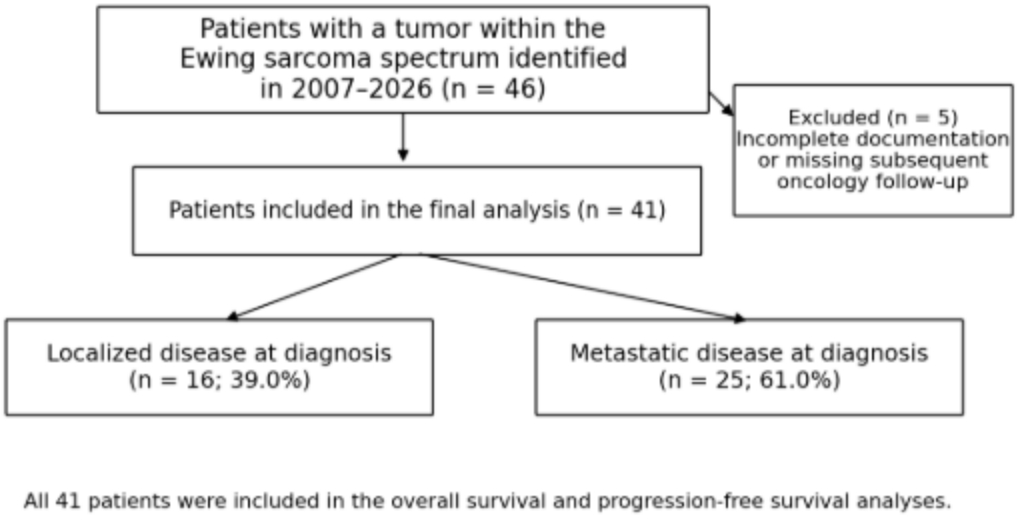


Figure 1

Flow diagram of patient selection for the retrospective cohort.

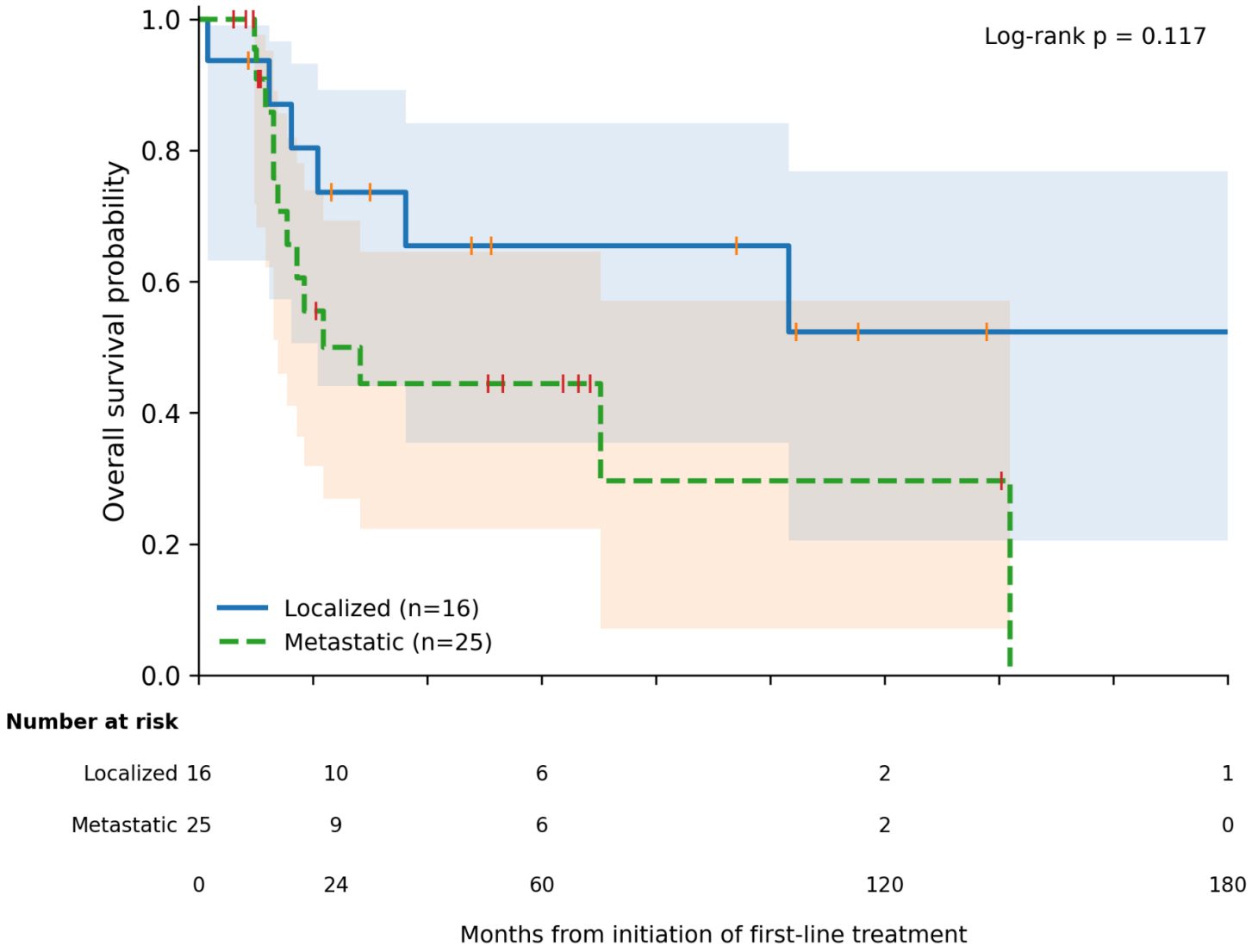


Figure 2

Overall survival according to disease extent at diagnosis. Shaded areas represent 95% confidence intervals, vertical marks indicate censored observations, and numbers at risk are shown below the plot. Log-rank P = .117.

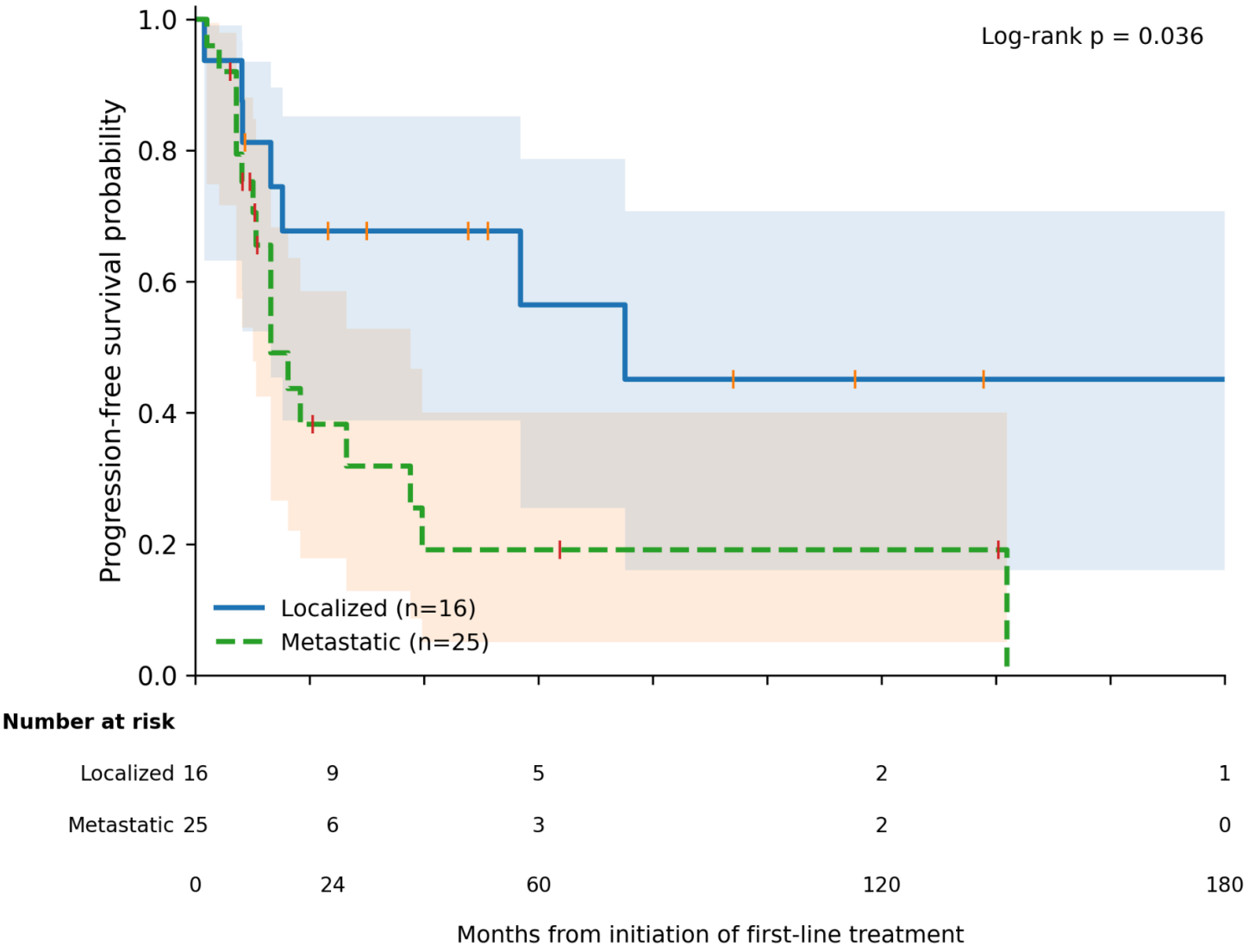


Figure 3

Progression-free survival according to disease extent at diagnosis. An event was progression, recurrence, or death from any cause. Log-rank P = .036.

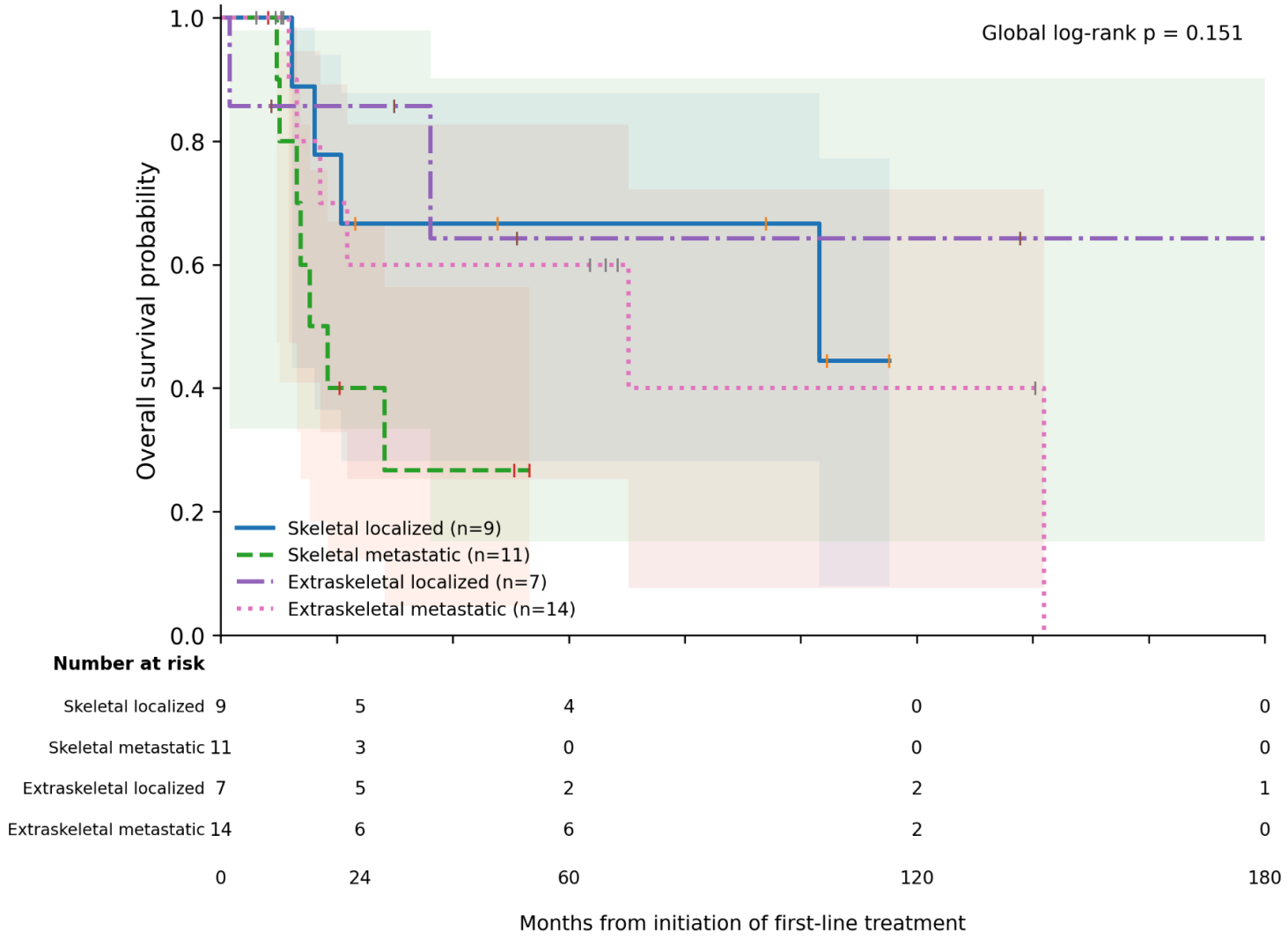


Figure 4

Overall survival across four clinical subgroups. Global log-rank P = .151.

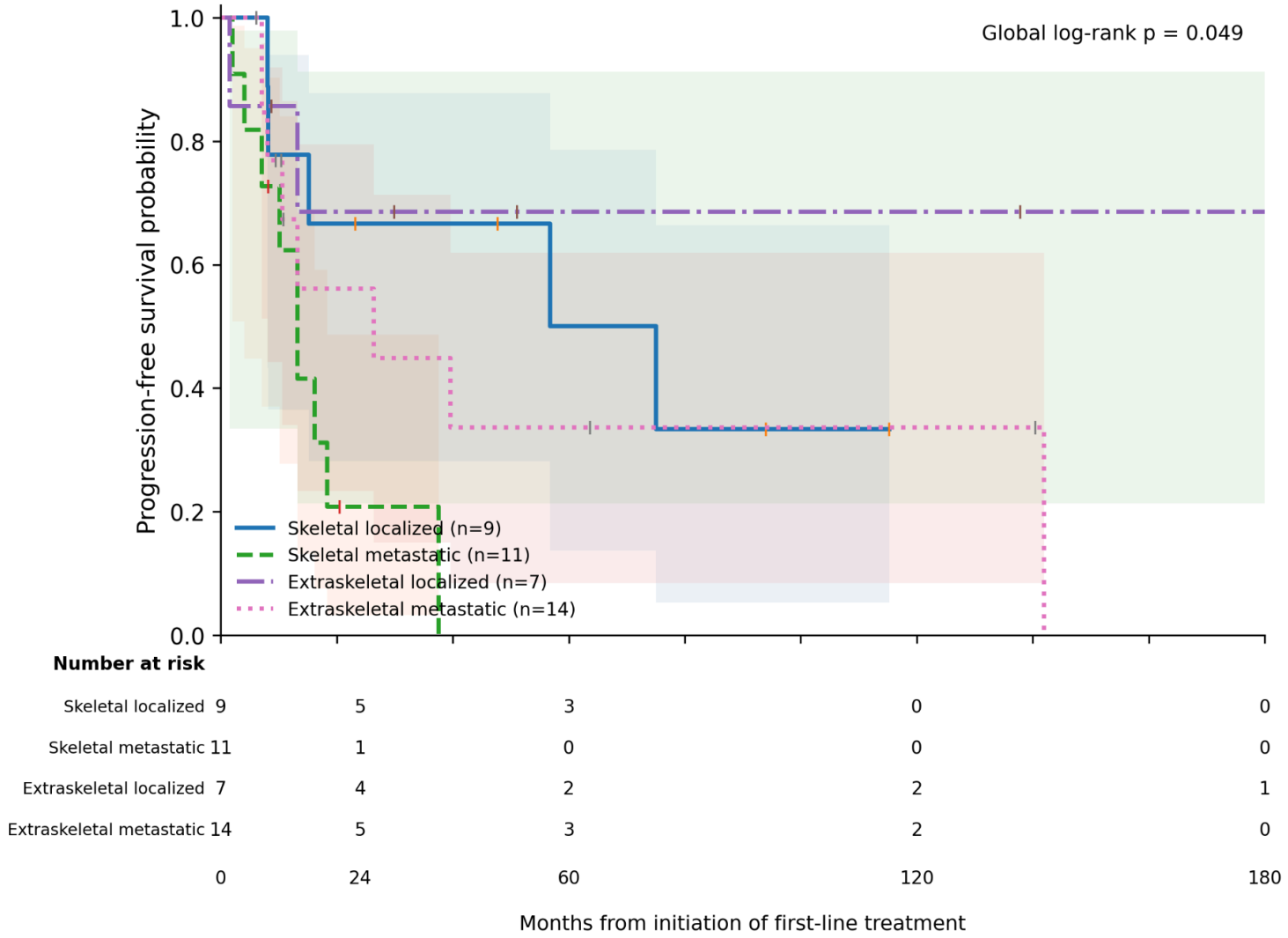


Figure 5

Progression-free survival across four clinical subgroups. Global log-rank P = .049.

Supplementary Files

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