Artigo original

20º CONGRESSO NACIONAL DE ONCOLOGIA - PREMIADO

Best oral presentation in the "Sarcoma" category

Neoadjuvant Concurrent Chemoradiation for High-Risk Adult Soft Tissue Sarcoma - 19 Years of a Single Institution Experience

Radioquimioterapia Neoadjuvante no Tratamento de Sarcomas de Tecidos Moles de Alto Risco – 19 Anos de Experiência de um centro

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Abstract

Introduction: *Although Surgery and Radiation therapy (RT) represent standard therapy in High-Risk Soft Tissue Sarcomas (HRSTS), its sequence remains controversial. Neoadjuvant chemoradiation improves survival in patients with HRSTS. Tumor size, surgical margins, and pathologic complete response (pCR) are prognostic factors with unknown significance.*

Material and Methods: *Retrospective analysis of 25 patients with stage III HRSTS, who underwent neoadjuvant treatment (2002-2020), with 16 receiving preoperative chemoradiation (Adriamycin 90mg/m² + Dacarbazine 900mg/m² + Ifosfamide 10mg/m² ± Vincristin 2mg bolus; 4500-5400cGy/25-30fr) and surgery. Clinical and pathologic data and treatment-related toxicities were assessed. Survival and univariate analyses were performed using Kaplan-Meier Method and Cox regression (α=0.05).*

Results: *Sixteen patients were included: 68.8% male, median age 44 [18-78] years. Median tumor size was 12 [5-25] cm and 68.8% were extremity sarcomas. Four (25%) patients had pleomorphic liposarcoma and 25% spindle cell sarcomas. Most patients (87.5%) had high-grade (G3) tumors. No patient interrupted RT. Median of 7 [5-10] chemotherapy cycles, with cycle postponement in 18.8% patients. Surgery (75% wide excision) occurred on a median of 2 [1-9] months after RT and was uncomplicated in 68.8% (25% wound dehiscence, 12.5% wound necrosis and 6.3% osteitis). Fourteen (87.5%) patients presented negative surgical margins (R0) and 25% pathologic complete response (pCR), with 60% of resected specimens showing ≥90% pathologic necrosis. Eight (50%) patients had hematological toxicity G3-4: 18.8% anemia; 50% leukopenia; 25% thrombocytopenia. Eleven (68.8%) patients presented radiation-induced dermatitis (62.5%, G1-2). For a median follow-up time of 6.3 years [8 months – 18 years], 3 and 5-year survival rates were: Overall Survival and Disease-Free Survival were equivalent (62.5% and 56.3%); Local Recurrence-Free Survival (LRFS) of 92.9%; Distant Disease-Free Survival of 68.8% and 61.9%; Disease-Specific Survival of 75% and 67.5%, respectively. Microscopic positive margins influenced LRFS (50% vs 100%; p=0.014). DSS was non-significantly influenced by pCR (p=0.161) and largest tumor dimension≤10cm (p=0.332).*

Conclusion: *Neoadjuvant chemoradiation is an acceptable strategy in HRSTS, with comparable survivals to reported data and manageable acute toxicity. Complete resection rates were high and associated with improved LRFS. Smaller tumors (≤10cm) and achieving pCR appears to be favorable prognostic factors.*

Key-words: *Sarcoma; Radiotherapy; Drug therapy; Neoadjuvant Therapy.*

Resumo

Introdução: Embora cirurgia e radioterapia (RT) sejam terapêutica standard nos Sarcomas de Tecidos Moles de Alto Risco (STMAR), a sua sequenciação permanece controversa. A radioquimioterapia neoadjuvante (RQTNA) melhora a sobrevivência em doentes com STMAR. Tamanho tumoral, margens cirúrgicas e resposta patológica completa (pCR) são fatores prognósticos com significância desconhecida.

Material e Métodos: Análise retrospetiva de 25 doentes com STMAR estádio III, submetidos a tratamento neoadjuvante (2002-2020), dos quais 16 realizaram RQTNA (Adriamicina 90mg/m^2 + Dacarbazina 900mg/m^2 + Ifosfamida 10mg/m^2 ± Vincristina 2mg bolus); 4500-5400cGy/25-30fr) e cirurgia. Avaliação de dados clínico-patológicos e toxicidades. Análise de sobrevivências e univariada pelo método *Kaplan-Meier* e Regressão de Cox (α=0,05).

Resultados: Incluídos 16 doentes: 68.8% sexo masculino, idade mediana 44 [18-78] anos. Dimensão mediana de 12 [5-25] cm, sendo 68.8% sarcomas dos membros. Quatro (25%) doentes com lipossarcoma pleomórfico e 25% fusocelular. A maioria (87,5%) dos doentes com tumores de alto grau (G3). Nenhum interrompeu a RT. Mediana de 7 [5-10] ciclos de QT, com adiamento em 18,8% dos doentes. A cirurgia (75% resseção alargada) decorreu, em mediana, 2 [1-9] meses após RT, sem complicações em 68,8% (25% deiscência da sutura, 12,5% necrose da ferida operatória e 6,3% osteíte). Quatorze (87,5%) doentes apresentaram margens cirúrgicas negativas (R0) e 25% pCR, com 60% das peças operatórias a mostrar ≥90% necrose patológica. Em 8 (50%) doentes foi registada toxicidade hematológica G3-4: 18.8% anemia; 50% leucopenia; 25% trombocitopenia. Onze (68,8%) doentes apresentaram radiodermite (62,5% G1-2). Com 6.3 anos [8 meses – 18 anos] de follow-up mediano, as sobrevivências (3 e 5 anos) foram: Sobrevivência Global e Sobrevivência Livre de Doença equivalentes (62,5% e 56,3%); Sobrevivência Livre de Recorrência Local (SLRL) 92,9%; Sobrevivência Livre de Metastização 68,8% e 61,9%; Sobrevivência Específica de Doença (SED) 75% e 67,5%, respetivamente. Margens positivas influenciaram a SLRL (50% *vs* 100%; p=0.014). A SED foi influenciada pela pCR (p=0,161) e tamanho tumoral ≤10 cm (p=0,332).

Conclusão: A RQTNA é uma estratégia aceitável em STMAR, com sobrevivências comparáveis às reportadas na literatura e toxicidade aguda manejável. A taxa de resseções completas foi elevada, associando-se a melhor SLRL. Tumores mais pequenos (≤10cm) e pCR parecem ser fatores prognósticos favoráveis.

Palavras-chave: Sarcoma; Radioterapia; Quimioterapia; Terapêutica Neoadjuvante.

Introduction

Soft tissue sarcomas (STS) are a heterogeneous group of solid tumors, comprised of more than 50 histopathologic subtypes. Factors including histologic grade, tumor size, and superficial versus deep anatomic location are of prognostic importance.[1–4] High-risk soft tissue sarcomas (HRSTS) are defined by tumors greater than 5cm in size and intermediate to high grade. Some histologic types are classified as high grade, such as synovial sarcoma, rhabdomyosarcoma, and Ewing sarcoma.[5–7]

Although surgical resection stands as the standard primary treatment for most patients with STS, larger tumor size, location or proximity to critical normal tissues may lead to positive margins, associated with higher rates of local recurrence (LR).[1,2,6] The addition of radiation therapy (RT) allows less radical surgical approaches, with limb, muscle, or organ function preservation, and improves local control of the primary STS site.[1–3,7,8]

Besides LR risk, patients with HRSTS are at a higher risk of systemic recurrence and mortality, despite optimal local treatment.[5,6,9–11] Thus, the addition of neoadjuvant or adjuvant chemotherapy (ChT) may improve disease-free survival (DFS) and overall survival (OS).[1,2,6,11,12]

Although ideal treatment sequencing is yet to be determined, potential benefits associated with neoadjuvant concurrent chemoradiation include: fewer late toxicity and an improved long term functional outcome, due to lower radiation dose given to a smaller tissue volume compared to the adjuvant setting;[13,14] a lower risk of tumor seeding during surgical manipulation, easing resection and decreasing LR;[1,14] and the possibility to assess treatment response, such as treatment-induced pathologic necrosis, a known prognostic factor for clinical outcomes, guiding adjuvant treatments.[6,15]

As such, preoperative chemoradiation is an appropriate strategy to be considered in patients with localized extremity and superficial trunk HRSTS.[1,2,6,9,10] However, this treatment approach has been associated with non-negligible acute toxicities, with increased risk of postoperative wound complications,[1,2,4,9,13,14] and frequent grade 3 or 4 hematologic toxicity in the preoperative period.[6,7,9]

The aim of this study was to report demographic and clinical characteristics, short-term complications, and outcomes of patients with HRSTS treated with preoperative chemoradiation and surgery in our institution.

Materials and Methods

We retrospectively reviewed 25 patients with HRSTS of the extremity or superficial trunk, 16 of whom were treated with neoadjuvant concurrent chemoradiation followed by surgery in our center, between January 2002 and December 2020. This study excluded 9 patients who did not receive ChT or surgery or who were found to have non-localized disease (**Fig. 1**).

Patients with American Joint Committee on Cancer (AJCC) 8th edition clinical Stage III (cT2–4N0M0) histology-proven HRSTS were enrolled. High-risk tumors were defined by large lesions (5cm or more in maximal dimension) of intermediate or high histologic grade.

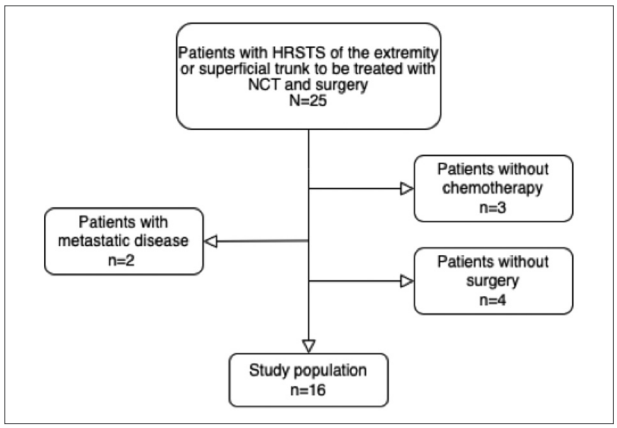

Figure 1. Flowchart of all excluded and included patients. HRSTS, high risk soft tissue sarcoma; NCT, neoadjuvant concurrent therapy.

Patients included had an initial imaging of their primary tumor with either Magnetic Resonance Imaging (MRI) or Computed Tomography (CT). A CT of the thorax, abdomen, and pelvis or a fluorodeoxyglucose (FDG)-positron emission tomography (PET) scan were used to screen for distant metastasis, as part of initial staging workup. Pre-operative therapy with concurrent chemoradiation then followed. Restaging with CT and/or MRI were performed prior to surgery.

A simulation CT scan, with custom immobilization using a thermoplastic mold was acquired. External-Beam Radiation Therapy (EBRT) Gross Tumor Volume (GTV) was defined using a CT – MRI image registration, allowing for superior soft tissue discrimination, better distinguishing tumor boundaries from the adjacent normal structures. The Clinical Target Volume (CTV) consisted of the GTV with an anatomically constrained margin (size depending on tumor location), encompassing peritumoral edema and biopsy tract, per the ASTRO Clinical Practice Guideline by Salerno *et al.*[3] Planning Target Volume (PTV) consisted of an isotropic expansion of 0.5 cm given the fact that Image-guided Radiation Therapy (IGRT) was used, with a Cone-Beam Computer Tomography (CBCT) acquisition before each treatment.

A dose-fractionation scheme of 4500-5400 cGy in 180-200cGy once daily fractions was prescribed. Treatments were planned using a PTV coverage primary goal of $V_{100\%} > 95\%$ and delivered using a 3-Dimensional Conformal Radiation Therapy (3D-CRT) or Volumetric Modulated Arc Therapy (VMAT) technique.

Concurrent ChT was initiated either before or at the time of radiation therapy. The ChT regimen consisted of pre-operative Adriamycin 90mg/m² + Dacarbazine 900mg/m² + Ifosfamide 10mg/m² ± Vincristine 2mg bolus on a 21-day cycle. Patients received intravenous hydration, mesna, and antiemetics per institutional guidelines. Growth factor support with pegfilgrastim was administered after each ChT cycle.

Surgery was planned to follow the completion of chemoradiotherapy and was undertaken with limb sparing intent, consisting, if possible, of wide excision with tumor-free margins and *en bloc* excision of the biopsy site. Limb amputation was considered if gross total resection of the tumor was expected to render the limb nonfunctional.

Resected specimens were evaluated by an expert pathologist for excision margin status. Re-resection was considered when positive margins were documented, and limb function would not be affected. Other features were assessed including the presence of necrosis, its approximate extent, and pathologic response to neoadjuvant chemoradiation.

After treatment protocol completion, patients were followed every 3 months for the first 3 years and every 6 months thereafter. Physical examinations were performed at each visit. Imaging with MRI was used to assess treatment response, followed by periodic imaging of primary site for locorregional recurrence detection. Imaging of chest and other know sites of metastatic disease was used for distant disease recurrence detection.

Patient medical records, including demographic information, pathology and radiologic reports and surgical records were reviewed. The following clinical and pathologic data were collected: age at diagnosis, sex, Karnofsky Performance Status (KPS), anatomic tumor location, largest tumor dimension, histologic grade (G) and tumor histology. Treatment data including RT delivery technique, Overall Treatment Time (OTT) and dose fractionation, ChT cycles and regimen and surgical complications were also gathered. Finally, surgical outcomes and pathologic findings, including surgical margin status, necrosis percentage and pathologic complete response (pCR), defined as 0% tumor viability in the final specimen after neoadjuvant treatment[15], were documented. Toxicity was evaluated using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Regarding the statistical analysis, outcomes measured were Overall Survival (OS), Disease Specific Survival (DSS), Disease-Free Survival (DFS), Locoregional Recurrence-Free Survival (LRFS) and Distant Disease-Free Survival (DDFS). OS was defined as the time from the beginning of pre-operative therapy to date of death and DSS from the beginning of pre-operative therapy to date of death from HRSTS. DFS was the time from the beginning of pre-operative therapy to lack of locoregional control or distant metastases. LRFS was the time from the beginning of pre-operative therapy to lack of locoregional control and DDFS to lack of distant metastases. To explore potential predictors of clinical outcome, univariate survival analysis was performed between each of the primary clinical outcomes and variables of interest, namely: surgical margin status, anatomic tumor location, largest tumor dimension (>10cm cutoff), percent pathologic response (≥50% and ≥90% cutoffs and pCR), age (>60 years cutoff) and number of ChT cycles completed (≥7 cycles cutoff). Survival curves were determined by the Kaplan-Meier method and univariate analyses were performed with the Cox regression. p-values were calculated using a significance threshold of 0.05. Statistical analyses were performed using IBM® SPSS® Statistics version 24.

Since this study complies with the principles of the Declaration of Helsinki, it was approved by the ethics committee of

the hospital and exempted of informed consent, owing to its retrospective nature.

Results

Patient characteristics

Patient and tumor clinicopathologic features are summarized in **Table 1**. Sixteen HRSTS patients were reviewed, with median age at diagnosis 44 years (range, 18-78 years), of whom 11 (68.8%) patients were male. The most common anatomic site were the extremities (68.8%) and pre-treatment median largest tumor dimension was 12 cm (range, 5-25 cm). Tumors were grade 3 in 14 (87.5%) patients and grade 2 in the remaining 2 (12.5%) patients. The two most common histologic subtypes were pleomorphic liposarcoma (25%, 4/16) and spindle cell sarcoma (25%, 4/16), followed by myxoid liposarcoma (12.5%, 2/16) and Ewing sarcoma (12.5%, 2/16).

Table 1. Patient characteristics.

Characteristic			Total
Age, years Median [Range]			**44 [18 - 78]**
Sex	Male		**11 (68.8%)**
	Female		**5 (31.2%)**
Karnofsky performance status (%) Median [Range]			**90 [90 - 100]**
Anatomic site	Extremity		**11 (68.8%)**
	Superficial trunk		**5 (31.2%)**
Largest tumor dimension, cm Median [Range]			**12 [5 - 25]**
Histologic Grade (G)	Intermediate (G2)		**2 (12.5%)**
	High (G3)		**14 (87.5%)**
AJCC clinical stage (cT)	cT2		**6 (37.5%)**
	cT3		**4 (25%)**
	cT4		**6 (37.5%)**
Tumor histology	Liposarcoma	Myxoid	**2 (12.5%)**
		Pleomorphic	**4 (25%)**
	Spindle cell sarcoma		**4 (25%)**
	Ewing sarcoma		**2 (12.5%)**
	Leiomyosarcoma		**1 (6.3%)**
	Synovial		**1 (6.3%)**
	Undifferentiated sarcoma		**1 (6.3%)**
	Clear cell sarcoma/NOS		**1 (6.3%)**
Total			**16 (100%)**

NOS, not otherwise specified.

Treatment received

An overview of treatment characteristics is shown in **Table 2**.

Patients received neoadjuvant radiation either by 3D-CRT (87.5%, 14/16) or VMAT (12.5%, 2/16) technique. Median OTT was 41 days (range, 31-49 days), with no treatment interruption or suspension observed. Most patients received a total dose of 5040cGy/28F (43.8%, 7/16) or 5000cGy/25F (37.5%, 6/16). Other dose prescriptions included 4500cGy/25F in 2 (12.5%) patients or 5040cGy/30F in 1 (6.3%) patient.

Table 2. Surgical and pathologic outcomes.

			Total
Surgical procedure	Limb-sparing	Wide resection	**2 (12.5%)**
		Marginal resection	**4 (25%)**
	Amputation		**4 (25%)**
Microscopic margins	R0 (negative)		**14 (87.5%)**
	R1 (positive)		**2 (12.5%)**
Pathologic response	≥ 50%		**14 (87.5%)**
	≥ 90%		**9 (60%)**
	100% (pCR)		**4 (25%)**
Total			**16 (100%)**

pCR, pathologic complete response.

All patients received concurrent chemoradiation, with a median of 7 ChT cycles (range, 5-10 cycles) received. Twelve (75%) patients completed a median of 4 cycles (range, 1-7 cycles) prior to radiation therapy initiation. Eleven (68.8%) patients still underwent at least one ChT cycle after radiation therapy completion, with a median of 3 cycles (range, 1-6 cycles) received.

Surgery was performed after a median of 2 months (range, 1-9 months) after radiation therapy completion. Twelve (75%) patients underwent wide resection, 3 (18.8%) patients underwent marginal resection, and 1 (6.3%) patient underwent amputation as gross total resection was expected to render high morbidity. Negative (R0) margins were achieved in 14 (87.5%) patients. Two (12.5%) patients had microscopic positive margins (R1) and did not underwent re-resection for R0 margins as it was not considered feasible. Pathologic response evaluation revealed a pathologic complete response (pCR) in 4 (25%) patients. Nine (60%) patients had ≥90% tumor necrosis evaluated in the surgical specimen and 14 (87.5%) patients had ≥50%.

Chemoradiation toxicities and wound complications

Treatment-related toxicities are summarized in **Table 3**.

Radiation-induced dermatitis (RID) (grade 1 or 2) was observed in 9 (56.3%) patients and 1 (6.3%) patient presented RID grade 3.

Regarding grade > 2 chemotherapy-related acute hematologic toxicities, 3 (18.8%) patients presented grade 3 anemia, 8 (50%) patients presented leukopenia grade 3 or 4 and 4 (25%) patients presented thrombocytopenia grade 3 or 4. Three (18.8%) patients had to postpone at least one ChT cycle due to hematologic toxicities. Six (37.5%) patients reported grade 1 or 2 nausea and vomiting.

Overall, wound complications occurred in 5 (31.3%) patients. Wound dehiscence requiring local wound care was observed in 4 (25%) patients, and wound necrosis occurred in 2 (12.5%) patients, who were treated with debridement. Osteitis occurred in 1 (6.3%) patient, requiring combination of surgery and antibiotics.

No treatment-related deaths or secondary myelodysplasias were reported.

Table 3. Treatment-related toxicities.

Characteristic			Grade 1-2	Grade 3	Grade 4	Total
Radiation-induced dermatitis			**10 (62.5%)**	**1 (6.3%)**	**0**	**11 (68.8%)**
Hematologic toxicity	Anemia		**13 (81.3%)**	**3 (18.8%)**	**0**	**16 (100%)**
	Leukopenia		**7 (43.8%)**	**5 (31.3%)**	**3 (18.8%)**	**15 (93.8%)**
	Thrombocytopenia		**5 (31.3%)**	**1 (6.3%)**	**3 (18.8%)**	**9 (56.3%)**
	Total		**8 (50%)**	**4 (25%)**	**4 (25%)**	**16 (100%)**
Nausea and vomiting			**6 (37.5%)**	**0**	**0**	**6 (37.5%)**
Wound complications	No		**11 (68.8%)**			**11 (68.8%)**
	Yes	Wound dehiscence	**4 (25%)**			**5 (31.3%)**
		Wound necrosis	**2 (12.5%)**			
		Osteitis	**1 (6.3%)**			

Survival analysis

At a median follow-up time of 6.3 years (range, 8 months – 18 years), 7 (43.8%) patients had died, 5 of whom (31.3%) due to sarcoma. Nine (56.3%) patients were alive and without evidence of local or distant disease. One (6.3%) patient had evidence of local recurrence and 6 (37.5%) patients of distant metastatic disease, of which 4 (25%) with pulmonary metastases and 2 (12.5%) with bone metastases. The 3- and 5-year survival rates for LRFS were 92.9%, for DDFS were 68.8% and 61.9%, and for DFS were 62.5% and 56.3%, respectively (**Fig. 2.A, B, C**). Regarding DSS, 3- and 5-year survival rates were 75% and 67.5%, and OS 3- and 5-year survival rates were 62.5% and 56.3%, respectively (**Fig. 2.D, E**).

No significant associations were found between LRFS, DDFS, DFS, DSS or OS and anatomic tumor location, largest tumor dimension (>10cm cutoff), percent pathologic response (≥50% and ≥90% cutoffs and pCR), age (>60 years cutoff) or number of ChT cycles completed (≥7 cycles cutoff). However, pCR was associated with a trend towards improved DSS, with 5-year survival rates for patients achieving pCR of 100% and 57.1% for patients not achieving pCR (*p*=0.161) (**Fig. 3.A**).

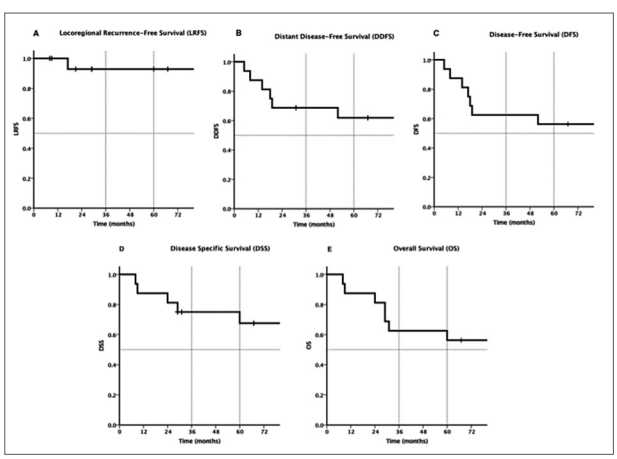

Figure 2. Kaplan-Meier estimates of (A) Locoregional Recurrence-Free Survival (LRFS), (B) Distant Disease-Free Survival (DDFS), (C) Disease-Free Survival (DFS), (D) Disease Specific Survival and (E) Overall Survival (OS).

Largest tumor dimension ≤10cm showed a non-significant favorable influence in 5-year DSS (83.3% vs. 58.3%, p=0.332) and in 5-year DDFS (83.3% vs. 50%, *p*=0.242) (**Fig. 3.B, C**). Although surgical margin status significantly influenced LRFS, with 5-year survival rates for negative margins of 100% and 50% for positive margins (*p*=0.014) (**Fig. 3.D**), such association has limited statistical significance, given that only 2 (12.5%) patients presented with positive margins, 1 (6.3%) of whom subsequently showing evidence of local recurrence.

Discussion

Patients with HRSTS are at higher risk for distant metastatic progression and local recurrence if appropriate resection margins are not achieved.[12] Consequently, the addition of RT and ChT to sur-

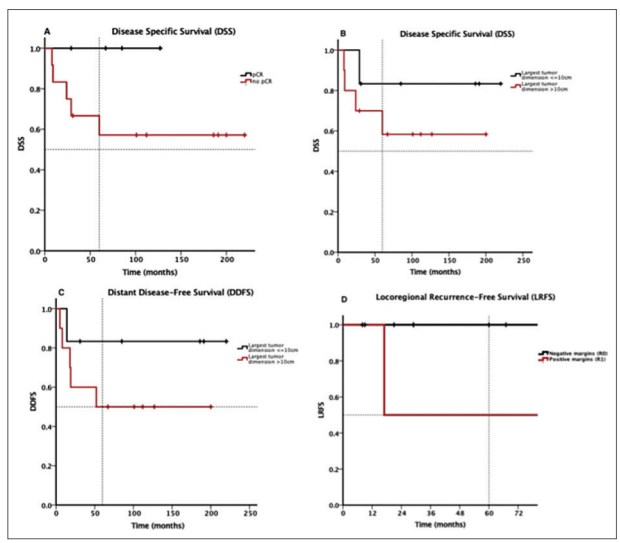

Figure 3. Disease Specific-Survival (DSS) for patients presenting with pathologic complete response (pCR) vs. without pCR (A) and for patients with largest tumor dimension ≤ 10cm vs. >10cm (B). Distant Disease-Free Survival (DDFS) for patients with largest tumor dimension ≤ 10cm vs. >10cm (C). Locoregional Recurrence-Free Survival (LRFS) for patients with negative surgical margins (R0) vs. positive margins (R1)

gical resection has been shown to improve oncological outcomes, with ideal timing of its delivery still to be determined.[1,2,8,11,13]

In this analysis in patients with localized extremity and superficial trunk HRSTS treated with neoadjuvant chemoradiation followed by surgery, we report promising 5-year rates of both local (LRFS 92.9%) and distant disease control (DDFS 61.9%), equivalent to previous studies using similar treatment protocols.[9,11,12] Five-year DFS and OS were both 56.3%, and were relatively similar to the Phase II multi-institutional RTOG study 95-14 results.[11] Other studies reported higher 5-year DFS and OS outcomes having, however, an inferior median follow-up time (46 – 48 months).[9,12,16]

Preoperative chemoradiation enables the assessment of pathologic response, the most objective measure of sensitivity to neoadjuvant therapy, and a known prognostic factor for DFS and OS, that allows for adjuvant therapy guidance.[2,15] In our review, most patients showed 90% or more pathologic necrosis. Although not statistically significant, pCR was associated with better DSS outcomes, with no patients who presented with pCR having local or distant disease recurrence. Furthermore, the administration of neoadjuvant (*vs* adjuvant) therapy facilitates complete surgical resection, allowing limb preservation[2,9,13] and reducing local recurrence rates.[12,14,17] Our study documented high percentage of patients with negative surgical margins, significantly improving LRFS. However, due to the reduced number of patients included, one of the main limitations of this review, this conclusion has limited statistical significance. Finally, tumor size, a variable already considered in staging systems, is also a prognostic factor, with patients with large extremity lesions having an increased risk of developing distant metastases.[5,16,17] Our results also reflect this association, with a tendency for patients presenting with lesions greater than 10cm having poorer DDFS and DSS.

Although preoperative chemoradiation is associated with significant short-term toxicities,[1,9,11,18] the ones observed in this study were manageable. In fact, despite a high percentage of patients presenting with treatment-related hematologic toxicities, most were transitory grade 3 or inferior, with only 18.8% of patients reporting grade 4 leukopenia or grade 4 thrombocytopenia, leading to a minor ChT cycle postponement. More importantly, no toxicities grade 5 were observed, as opposed to RTOG 95-14 study.[11]

Regarding skin toxicity, lower percentages and intensities were also reported in this study compared to RTOG 95-14 results, with only 6.3% patients presenting with grade > 2 radiation-induced dermatitis. The use of CT – MRI image fusion for clinical volume definition, a smaller RT field design to the one used in the RTOG 95-14 protocol[12], and daily IGRT enabling reduced PTV margins, may have contributed to diminished tissue toxicity.[3,12]

In this review, the rate of wound complications was 31.3%, which aligns with percentages reported in previous studies (32% - 43%).[8,13,14,18] Being the higher risk of postoperative wound complications one of the main disadvantages of preoperative chemoradiation, comparing to its delivery in the adjuvant setting[1,2,13], these results are reasonable, especially when we consider that the majority were minor complications and did not require a secondary surgical intervention.

This study was, as previously stated, limited by its small study population, thus being underpowered for detection of significant associations between patient or tumor-related factors and clinical outcomes. Besides, it is a single-institution analysis, with a retrospective design, that did not compare the described regimen to a control group. Systemic therapy was administered at the discretion of the assistant medical oncologist, with a wide variation in the timing of initiation, total number of cycles and drug combination (within the referred protocol). Adjuvant systemic therapy was also not considered and certainly influenced the reported clinical outcomes. Finally, the heterogeneity of tumor histology included also limits conclusions, as each subtype might behave differently regarding treatment response or patterns of disease recurrence.[15]

Conclusions

Preoperative chemoradiation is a valid treatment strategy for HRSTS, allowing for high rates of complete limb-sparing resections. Promising local and distant disease control rates were observed and are comparable to published survival outcomes. Acute hematologic toxicities reported were acceptable and less severe than previous studies. The use of modern simulation, planning and delivery RT techniques enables reduced treatment volumes and may have contributed to diminished tissue toxicity. However, multi-institutional prospective randomized trials are needed to further investigate potential benefits of this treatment strategy compared to adjuvant chemoradiation, regarding survival rates, short and long-term toxicity.

Contributorship Statement / Declaração de Contribuição:

TD: Study design, retrospective data collection, data analysis and interpretation, manuscript writing, manuscript revisions

AS: Study design, critical review and manuscript revisions, project supervision.

PT: Retrospective data collection, data analysis and interpretation, manuscript writing, manuscript revisions.

LM: Retrospective data collection, manuscript revisions.

IP: Retrospective data collection, manuscript revisions.

BF: Data analysis and interpretation, critical review and manuscript revisions.

JC: Manuscript revisions.

MB: Manuscript revisions, project supervision.

All authors have read and agreed to the published version of the manuscript/ todos os autores leram e aceitaram a versão publicada do manuscrito.

TD: Desenho do estudo, recolha restrospetiva de dados, análise e interpretação de dados, elaboração do manuscrito, revisão do manuscrito.

AS: Desenho do estudo, revisão crítica e alterações ao manuscrito, supervisão do projeto.

PT: recolha restrospetiva de dados, análise e interpretação de dados, elaboração do manuscrito, revisão do manuscrito

LM: recolha restrospetiva de dados, revisão do manuscrito.

IP: recolha restrospetiva de dados, revisão do manuscrito.

BF: recolha restrospetiva de dados, revisão crítica e alterações ao manuscrito.

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