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Histopathological tumor response following neoadjuvant hyperthermic isolated limb perfusion in extremity soft tissue sarcomas: Evaluation of the EORTC-STBSG response score

Marc G. Stevenson [a], Harald J. Hoekstra [a], Wangzhao Song [b], Albert J.H. Suurmeijer [b], Lukas B. Been [a, *]

[a] Department of Surgical Oncology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands
[b] Department of Pathology and Medical Biology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

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ABSTRACT

Introduction: This study aims to evaluate the applicability and prognostic value of the European Organization for Research and Treatment of Cancer-Soft Tissue and Bone Sarcoma Group (EORTC-STBSG) histopathological response score in extremity soft tissue sarcoma (ESTS) patients treated with neoadjuvant hyperthermic isolated limb perfusion (HILP) and delayed surgical resection.

Methods: Patients treated between 1991 and 2016 were included. The histopathological tumor response was established in accordance with the EORTC-STBSG response score. The distribution of patients was assorted according to the 5-tier histopathological response score for tumor grade, histological subtype and HILP regimen. Predictors for local recurrence free survival (LRFS) and overall survival (OS) were identified through Kaplan-Meier and Cox regression analyses.

Results: Ninety-one patients were included and their resection specimens were reanalyzed. Which resulted in 11 Grade A (12.1%), ten Grade B (11.0%), 15 Grade C (16.5%), 22 Grade D (24.2%) and 33 Grade E (36.3%) responses found among the series. The histopathological response was significantly influenced by the HILP regimen used, $p = 0.033$. Median follow-up was 65.0 (18.0–157.0) months. The histopathological response was not associated with LRFS nor OS. Resection margins, HILP regimen and adjuvant radiotherapy were associated with LRFS. Patients' age, tumor grade, tumor size and histological subtype were predictors for OS.

Conclusions: The EORTC-STBSG response score is applicable for determining the histopathological response to neoadjuvant ESTS treatment. However, this response does not seem to predict LRFS nor OS in locally advanced ESTS.

Introduction

Soft tissue sarcomas (STS) are relatively rare and heterogeneous tumors, including over 50 histopathological subtypes [1]. Approximately 50–60% of the STS arise in the extremities [2]. In the Netherlands, 600–700 patients are diagnosed with a STS leading to 300 STS related deaths annually [3,4].

Extremity soft tissue sarcomas (ESTS) patients' survival is mainly determined by metastatic potential, whereas local tumor treatment is of lesser importance. Consequently, local tumor treatment has evolved from amputation to limb salvage surgery combined with radiotherapy [5,6]. At presentation, some ESTS are considered to be locally advanced. Since the overall survival of ESTS patients is not increased by amputation of the affected limb [5], neoadjuvant hyperthermic isolated limb perfusion (HILP), followed by surgical resection, has been used to prevent amputation in locally advanced ESTS in over 40 centers throughout Europe [7,8], resulting in a limb salvage rate of 80–90% [9–12].

Apart from neoadjuvant HILP, preoperative radiotherapy has been used in ESTS for decades. More recently, neoadjuvant

* Corresponding author. University of Groningen, University Medical Center Groningen, Department of Surgical Oncology BA31, PO Box 30.001, 9700 RB, Groningen, The Netherlands.
E-mail address: l.b.been@umcg.nl (L.B. Been).

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chemotherapy has been tested in clinical trials in high-risk, but localized STS [13,14]. To evaluate the histopathological response to these neoadjuvant treatment strategies, a standardized approach for the pathological examination of pretreated sarcomas was proposed by the European Organization for Research and Treatment of Cancer-Soft Tissue and Bone Sarcoma Group (EORTC-STBSG) in 2016 [15]. This protocol includes a 5-tier response score based on the percentage of stainable, potentially viable tumor cells, clearly different from earlier methods in which the percentage of tumor necrosis was scored to determine the tumor response. Notably, thus far, data from the literature did not prove that the amount of tumor necrosis is prognostic in pretreated STS [15,16]. As tumor necrosis can be present in some STSs at diagnosis, it seems trustworthy to use the percentage of stainable cells in determining the histopathological response to neoadjuvant treatment. Recently, the first study applying the EORTC-STBSG response score found that it has no prognostic value with respect to recurrence free- and overall survival in a cohort of 100 extremity and trunk STS patients treated with radiotherapy prior to surgical resection [17].

This single tertiary sarcoma-center study aims to assess the applicability and the prognostic value of the EORTC-STBSG response score in locally advanced ESTS patients treated with neoadjuvant HILP followed by surgical resection of the residual tumor.

Patients and methods

Patients

The Institutional Review Board approved this study (case-number 2017-319). All consecutive patients over 18-years of age, with primary or recurrent, localized ESTS treated with neoadjuvant HILP followed by surgical resection, after 6–8 weeks, at the University Medical Center Groningen (UMCG) between 1991 and 2016 were analyzed. None of the patients were treated with neo-adjuvant chemotherapy. Patients' characteristics were obtained through medical record review. Patients for whom the required biopsy/tumor specimen was not available or not suitable for reanalyzes were excluded from the cohort.

Hyperthermic isolated limb perfusion

The HILP technique used, is based on the technique developed by Creech et al. [18] and has previously been described in more detail [19]. Under general anesthesia the major artery and vein of the affected limb were isolated and cannulated, thereby, isolating the blood flow of the limb from the systemic circulation. The cannulas were connected to an extracorporeal circuit. Subsequently, a tourniquet was applied to minimize leakage of the cytostatic agents into the systemic circulation. At the beginning, the perfusate consisted of interferon-γ (IFN-γ), tumor-necrosis factor-α (TNF-α) (Beromun®, Boehringer-Ingelheim GmbH, Vienna, Austria) and melphalan (Alkeran®, GlaxoSmithKline Pharmaceuticals, Research Triangle Park, NC, USA). IFN-γ was soon abandoned, due to its ineffectiveness [7,9]. Potential leakage of the cytostatic agents into the systemic circulation was continuously monitored by a precordial scintillation detector and I^{131}-human serum albumin [20,21]. To perform the perfusion under controlled mild hyperthermia (38.5–40.0 °C), the limb was externally heated. Due to improvements in the HILP treatment, not all patients in this series were treated according the same HILP regimen. IFN-γ was abandoned, the TNF-α dose was reduced and the perfusion time was shortened [11]. Until 2001 the perfusion duration was 90 min whereas from 2001 till now the duration was 60 min. The 90 min regimen was divided in 30 min of TNF-α perfusion, followed by 60 min of melphalan perfusion. The 60 min regimen, started with 15 min of TNF-α perfusion, then the melphalan was added and after another 45 min the perfusion was ended. Nowadays, 2 mg TNF-α is used for femoral and iliac perfusions. Whereas 1 mg TNF-α is used for upper extremity and popliteal perfusions. These TNF-α doses are lower than the formerly used 3–4 mg TNF-α [11]. The melphalan dose was based on the limb volume, 10 mg/L for upper extremity and popliteal perfusions, and 13 mg/L for iliac and femoral perfusions. Following the perfusion, the limb was flushed with saline, 2 L for upper extremity and popliteal perfusions, and 6 L for iliac and femoral perfusions. Following the flushing of the limb, the limb was filled with 1 U red blood cell concentrate. Afterwards, the cannulas were removed, the vessels repaired and the heparin antagonized with protamine sulphate. A closed fasciotomy of the anterior compartment of the lower leg was performed to prevent a compartment syndrome [22,23]. The first 24 h following the procedure, the patient was closely observed in the medium care or intensive care unit.

Methods

Prior to treatment, core-needle biopsies were performed for typing and grading of the tumors according to 'American Joint Committee on Cancer' and 'World Health Organization (WHO)' criteria [1,24]. Tumor margins were classified according to the 'Union for International Cancer Control' R classification [25] i.e. R0 for microscopically free tumor margins, R1 for microscopically compromised margins and R2 for macroscopically compromised margins. As previously reported, the histopathological examination of STSs, including the determination of the percentage tumor necrosis of the resection specimens has been standardized at the UMCG since 1991 [10,11,26]. In 2017, all resection specimens were re-analyzed by a pathologist with special interest and expertise in STS, who was blinded for clinical outcome, to classify the histopathological tumor response in accordance with the 5-tier, stainable tumor cell based, EORTC-STBSG response score; Grade A, no stainable tumor cells; Grade B, single stainable tumor cells or small clusters (overall below 1% of the whole specimen); Grade C, ≥1%-<10% stainable tumor cells; Grade D, ≥10%-<50% stainable tumor cells; Grade E, ≥50% stainable tumor cells [15].

The influence of tumor grade, histological subtype and HILP regimen on the histopathological response was investigated by assorting patients' distribution for these parameters according to the five response grades. Histopathological responders were defined as having <10% stainable tumors cells, combining response grade A, B and C. The remaining patients were considered histopathological non-responders with response grade D or E. Uni- and multivariate survival analyses were performed to identify associations between patient, tumor and treatment characteristics and 10-year local recurrence free survival (LRFS) or 10-year overall survival (OS).

Statistical analyses

Data are presented as frequencies and percentages for discrete variables and median and inter quartile ranges (IQR) for continuous variables. None of the variables were normally distributed. The Mann-Whitney U and Kruskal-Wallis test were used to compare patients' distribution for tumor grade, histological subtype and HILP regimen according to their corresponding response scores. A p-value <0.05 was considered to indicate statistical significance. Oncological outcome was defined as time from date of HILP to event, either local recurrence or death. The Kaplan-Meier method and log-rank test were used for univariate survival analyses. Cox-regression was used to perform multivariate survival analyses. All potential predictors were included in a first multivariate cox-regression model. Backward selection was used, and predictors with a $p < 0.1$ were included in the final model. Hazard ratios (HR)

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