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Original article

Time interval between surgery and start of adjuvant radiotherapy in patients with soft tissue sarcoma: A retrospective analysis of 1131 cases from the French Sarcoma Group ☆

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ABSTRACT

Purpose: The aim of this study was to evaluate the impact of the time interval (TI) between surgery and adjuvant radiotherapy (RT) in soft tissue sarcoma (STS).

Methods and materials: Data from 1131 patients treated between 1990 and 2014 were retrospectively reviewed. Inclusion criteria were: limb or superficial trunk wall STS (R0 or R1 resection) and adjuvant RT. The impact of TI on 10-year local relapse-free survival (LRFS) and 10-year overall survival (OS) was analyzed using a Log-rank test and then Cox Model.

Results: The median TI was 82 days (range, 18–346). With a median follow-up of 235 months (range, 2–296 months), the 10-year LRFS was 57.5% (±2%) and the 10-year OS was 64.2% (±2%). With a TI of 19–39 days, 40–79 days, 80–119 days, and ⩾120 days, 10-year LRFSs were 65.3%, 55.5%, 56.9% and 61.2% ($p = 0.465$), and 10-year OSs were 72.8%, 60.7%, 66.4% and 62.1% ($p = 0.347$), respectively. After adjustment for the factors significantly ($p \leqslant 0.05$) associated with LRFS and OS, TI did not alter LRFS ($p = 0.182$) either OS ($p = 0.335$).

Conclusions: In this retrospective STS database study, the TI between surgery and start of adjuvant RT did not seem to affect outcomes.

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Soft tissue sarcoma (STS) is a rare tumor, accounting for less than 2% of all adult cancers [1]. However, this incidence may be underestimated due to heterogeneity, ubiquitous locations and the complexity of diagnosis needing pathological expertise and sometimes biological molecular confirmatory tests [2–4]. The standard treatment for localized high-grade extremity soft tissue sarcoma (ESTS) is "large-*en bloc* resection" combined with radiation therapy (RT). Adjuvant RT could be omitted in some cases of superficial, low grade and small size STS [5,6]. Indeed, when added to conservative surgery, RT showed a significant benefit for local control in three randomized trials [7–9]. The timing of this RT remains a matter of debate because a randomized study of preoperative versus postoperative RT in the treatment of ESTS did not find differences in local control or overall survival [10]. However, this study demonstrated that postoperative RT was associated with more late toxicities (such as joint stiffness, fibrosis or edema) whereas preoperative RT was associated with more early wound complications after surgery [10,11]. Because of the high rate of wound complications in the preoperative arm (35% vs 17%, $p = 0.01$), the trial was closed after the preplanned interim analysis.

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In everyday practice, a large portion of STS cases underwent surgery before being referred to expert centers, and then these cases could not be considered for formal preoperative RT. Therefore, RT is currently most frequently delivered as an adjuvant therapy.

The time interval (TI) between surgery and RT in STS is a major concern for several reasons. First, the standard of care involves several different treatment schedules that should be perfectly coordinated. Secondly, the prognostic value of this TI is not well established because there are three retrospective studies that have been published to date [12–14]. Two of these included a small number of patients [12–13], and the third one included a heterogeneous population [14]. Consequently, the impact of TI on cancer control is still based on expert opinion [15]. Finally, this question is often unanswered in daily clinical practice, mainly for patients who have a long TI between surgery and RT for various causes (e.g., delay in referral, wound complications and adjuvant chemotherapy). Therefore, we performed this retrospective study to assess the impact of TI between surgery and postoperative RT on outcomes of adult patients with a localized STS.

Methods and materials

French Sarcoma Group database and inclusion criteria

Patients included in this study were all enrolled in the retrospective French Sarcoma Group (FSG) database, also known as Conticabase, which is now interconnected with other databases in SarcomaBCB (https://conticabase.sarcomabcb.org). Each patient with a STS can be included in this multicenter database after signing an informed consent sheet. All of the cases are centrally reviewed by the members of the pathology committee of the FSG and data are updated every two years with an unlimited follow-up.

The inclusion criteria of the present study were as follows: age $\geqslant$18 years old, STS included in the Conticabase, tumors located in the extremities and superficial trunk, primary treatment as curative intent and adjuvant radiotherapy delivered.

The exclusion criteria were as follows: metastasis at diagnosis, initial treatment of a local recurrence, adjuvant brachytherapy, neoadjuvant chemotherapy or radiotherapy and a R2 surgery.

Patients, tumors and treatment characteristics

From January 1990 to April 2014, 1131 patients who met the inclusion criteria were included in the database. They were treated in 15 French sarcoma reference centers. In each center, a physician reviewed the patient files and checked the recorded data. The following variables were considered for analysis: TI between surgery and RT; patient characteristics (i.e., gender, age, previous cancer, and hereditary predisposition); tumor characteristics (i.e., histological grade, tumor size, tumor depth, histological subtype, tumor site, vessel tumor emboli, bone, cutaneous, muscular or neurovascular invasion and multifocality); treatment characteristics (i.e., first surgery outside the reference center, margins status, RT total dose, postoperative chemotherapy, time to first consultation in the reference center, TI between the histological diagnosis and the first surgery).Histological tumor types and subtypes were classified according to the World Health Organization (WHO) classification of tumors [16]. The Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC) grading system [17] was applied. Tumor depth was superficial or deep according to the involvement of the muscle fascia. Margin status was established using the recommendations from the FSG, meaning a collegial process with surgical and pathological reports [18]. The results were finally reported with the Union Internationale Contre le Cancer (UICC) R system: R0 (complete microscopic excision), R1 (microscopic residual disease) or R2 (macroscopic residual disease) [18]. Institutional board approval was obtained for this study.

Statistical analysis

The TI was considered to be the interval, in days, between the first surgical excision and the first day of RT. It was analyzed as a continuous variable and as a categorical variable. For the categorical data, the population sample was divided into four groups according to quartiles: group A (18–39 days between surgery and RT), group B (40–79 days), group C (80–119 days) and group D ($\geqslant$120 days).

The impact of TI between surgery and RT was analyzed first for the whole population (N = 1131) and then with a subgroup named "optimal management" (n = 714). In this subgroup, patients had a margin status R0 and received a RT total dose $\geqslant$50 Gy. The local recurrence-free survival (LRFS) rate and overall survival (OS) rate were calculated using the Kaplan–Meier method. This impact has been analyzed in univariate analysis on LRFS and OS using a Log-rank test when TI was categorical data and a univariate Cox model when TI was continuous data. Then, a multivariate analysis was performed with other significant ($p < 0.05$) predictive factors identified in univariate analysis for LRFS and OS, using a Cox model. After adjustment to these predictive factors, the impact of TI was analyzed for LRFS and OS using a Cox model.

For the "optimal management" subgroup, the same analyses were performed.

All analyses were performed using the IBM SPSS Statistics 13.0 software.

Results

Main characteristics of the study population

The main characteristics of the study population are summarized in Table 1. The median age was 60 years (range, 19–100 years). Ninety-six patients (8.3%) had a previous cancer and 16 (1.4%) had a type 1 neurofibromatosis. The median tumor size was 80 mm (range, 2–450 mm). Most of the patients had muscular involvement (598 patients, 52.9%) and had no cutaneous, bone or neuro-vascular invasion (526 patients, 46.5%; 779 patients, 68.9%; and 732 patients, 64.7%, respectively). Nine hundred and sixty patients (84.9%) had a unifocal tumor. The median RT dose was 54 Gy (range, 11–74 Gy).

The main characteristics of patients in "optimal management" subgroup are presented in Supplemental data, Table 1.

TI

The median TI between surgery and RT was 82 days (range, 18–346 days). There were 55 patients (4.9%) in the group A TI category, 358 patients (31.7%) in group B, 241 patients (21.3%) in group C and 222 patients (19.6%) in group D. The mean TI was 96 days (standard deviation, 51; Supplemental data, Fig. 1). The median follow-up time was 235 months (range, 2–296 months).

Survival

In the whole study population (N = 1,131), 363 patients had a local recurrence and 291 patients died. The five- and 10-year LRFS were 70.9% and 57.5%, respectively. The five- and 10-year OS were 78.1% and 64.2%, respectively. The median LRFS was 149 months (range, 127–170 months). The median OS was 216 months (range, 146–285 months).

In the "optimal management" subgroup (n = 714), 210 patients had a local recurrence and 172 patients died. The five- and 10-year LRFS were 74.5% and 60.1%, respectively. The five- and 10-year OS

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