Patients with primary localized high-grade sarcomas of the digestive tract excluding GIST : a retrospective study from the French sarcoma group

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Abstract

Introduction : **The natural history of localized high-grade sarcomas of the digestive tract (SDT) excluding GIST has been rarely considered owing to their low incidence and heterogeneity. We describe the histoclinical characteristics of SDT and correlate them with patients' outcomes.**

Methods : **We retrospectively collected medical files from a European database covering connective tissue tumors listed in Europe for about twenty years. Only untreated localized primary high-grade SDT were included. A central histological review was performed for each case. Patients' characteristics were compared and correlated with clinical outcomes.**

Results : **A total of 45 patients were identified. Leiomyosarcomas (LMS) and undifferentiated sarcomas (UDS) were predominant, the former having better overall survival (OS) and progression-free survival (PFS) while the latter having a worse outcome than the other histological types. Complete remission was obtained in 34 patients (75%) and was associated with male sex, age over 40 years and monofocal tumor. Complete surgery and LMS histology were associated with a better prognosis without any significant difference in baseline characteristics or in treatment modalities.**

Conclusion : **Complete surgery and histological type seem to be prognostic indicators of SDT. These results suggest the importance of treating these patients in a reference center.** (Acta gastroenterol. belg., **2017**, 80, **481-486**).

Key words : sarcoma, digestive tract, leiomyosarcoma, undifferentiated sarcomas

Introduction

Soft tissue sarcomas (STM) are a heterogeneous group of rare malignant tumors with various natural histories, genetics, prognostic factors and treatment sensitivities. They can occur in almost any anatomic site, are located predominantly in the extremities and metastasize preferentially to the lung and liver (1). In adult and pediatric populations, they represent 0.7-1% and 4-8% of all malignant tumors and 0.2% and 5% of all bone sarcomas, respectively (2,3). While considerable progress has been made in the characterization and treatment of gastrointestinal stromal tumors (GIST), the most common mesenchymal tumors of the gastrointestinal tract (4,5), data on other digestive sarcomas as a whole are sparse owing to their very low incidence and heterogeneity. Several case reports mentioning different histological types of sarcomas in different organs are available, but no large series have been reported. Therefore, we decided to conduct a retrospective study of all cases of digestive sarcomas (excluding GISTs) recruited over 20 years in a large European database (https://conticabase.sarcomabcb.org) in order to correlate clinical and pathological assessment with outcomes in this population.

Material and Methods

Study Design and Data Source

We retrospectively collected medical files from a European database named the Conticabase that covers connective tissue tumors listed in Europe for about twenty years. It was created in 2006 jointly with the Conticanet network (CONnective Tissue CAncer NETwork) whose aim is to improve knowledge regarding connective tissue tumors with a view to improving their treatment. The database contains anonymized information describing the tumor, treatment and follow-up as well as tumor sample availability and molecular biology analyses for mesenchymal tumors except GIST and bone tumors. In July 2104, The Conticabase had 72 participating centers throughout Europe and had collated a total of 13 037 tumors. From this cohort, we selected patients with sarcomas of the digestive tract diagnosed from December 1993 to May 2014. Were excluded GIST, primary STM of other location, tumors of intermediate grade malignancy, cases with incomplete data, recurrent presentation previously treated or metastatic at diagnosis (Fig. 1). Authorization was obtained from each center involved in the cohort.

Statistical Analysis

Categorical variables were described using counts and frequencies, and quantitative variables were described using medians and ranges. Patients' characteristics were

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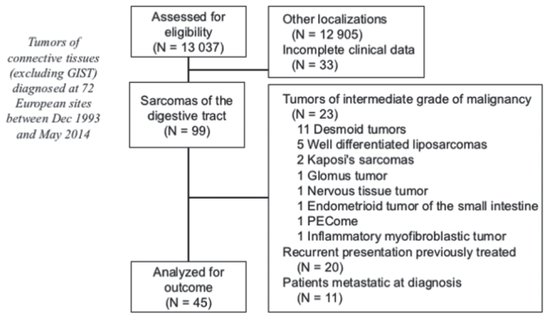

Figure 1. — Flow diagram showing selection of patients with localized sarcomas of the digestive tract.

compared with the χ^2 or the exact Fisher tests for discrete variables and the Rank-Wilcoxon test for continuous variables.

Overall survival (OS) was defined as the time from diagnosis to death. Progression-free survival (PFS) was defined as the time from diagnosis to progression/recurrence or death. To analyze recurrence-free interval (RFI), locoregional recurrence-free interval (LRFI) and distant recurrence-free interval (DRFI), we considered only patients with complete remission after initial treatment. For RFI, follow-up started at the date of histological diagnosis and continued until diagnosis of local or regional recurrence, distant recurrence or death, whichever appeared first. For LRFI, only local and regional diseases were considered as events. For DRFI, only distant metastases were considered as an event. OS, PFS, RFI, LRFI and DRFI rates were estimated using the Kaplan-Meier method and compared between groups with log-rank tests. Follow-up was estimated using the inverse Kaplan-Meier method.

The level of statistical significance was set at $\alpha = 0.05$. Statistical analyses were carried out with the SPSS® software version 17. We followed the reporting recommendations specified in the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) Statement (6).

Results

Characteristics of study population

A total of 45 patients with untreated localized sarcomas of the digestive tract were identified. 5 patients (11%) had a previous history of cancer. The locations of digestive sarcomas were different and involved the entire digestive tract (Table 1). Six tumors (14%) were multifocal but in the same part of the digestive tract. A central histological review done in a referral center of the French Sarcoma Group or of the RRePS Network (Reference Network in Pathology of viscera and soft tissue sarcomas, GISTs and desmoids tumors) was systematically performed for each case. As expected, histological subtypes were extremely heterogeneous, although leiomyosarcomas and undifferentiated sarcomas were clearly predominant, representing 54% and 23% of cases respectively. Tumor size ranged from 3 mm to 230 mm with a median size of 80 mm.

Forty-one (91%) primary tumors were resected (91.1%), 6 patients received (13.3%) adjuvant chemotherapy, 2 (4.4%) neoadjuvant chemotherapy and 6 (13.3%) post-operative radiotherapy. Complete remission was obtained in 34 patients (75%). Complete remission was associated with male sex (62 *vs.* 27%), age over 40 (91 *vs.* 64%), and monofocal tumor (94 *vs.* 64%) in univariate analysis. No other significant difference in patient or tumor characteristics was found (Table 1).

Overall survival (OS)

As of July 2014, the median follow-up of all groups of patients was 22.8 months (95% CI [0.66-198.2]). During the follow-up, 8 patients died. Median OS was not reached (Fig. 2A), and 2- and 5-year OS rates were estimated at 85% and 63.9%, respectively. Considering histological types, leiomyosarcomas had a significantly better OS (2-year OS rate estimated at 100%) than other subtypes (2-year OS rate of 75%), $p = 0.005$; and undifferentiated sarcomas significantly lower (2-year OS rate of 57%), $p = 0.001$.

Progression-free survival (PFS)

Median PFS was 46 months (95% CI [28-63]). The PFS rates at 2 and 5 years were 73% and 40%, respectively (Fig. 2B). Like OS, PFS was significantly better in leiomyosarcomas (2-year PFS rate of 72%) than undifferentiated sarcomas (2-year PFS rate of 34%), $p = 0.001$. Microscopically negative margins (R0) were associated with better PFS in univariate analysis, with a median PFS not reached in R0 resections *vs.* 9 months in R1 resection (95% CI [0-23.4] ; $p = 0.028$) and a 2-year PFS rate of 69.7 *vs.* 33.3%.

Recurrence-free interval (RFI)

The analyses of recurrence-free interval (RFI), locoregional recurrence-free interval (LRFI) and distant recurrence-free interval (DRFI) were done only in the group of 34 patients with complete remission after initial treatment. The median follow-up of patients was 23.6 months (95% CI [0.66-198.2]). Median RFI was 55 months (95% CI [29.7-80.3]). The RFI rates at 2 and 5 years were 66% and 44%, respectively (Fig. 3A). Criteria associated with a better RFI were female sex (median not reached *vs.* 38 months (95% CI [0.8-75.2]) ; $p = 0.024$), leiomyosarcoma histology (median not reached *vs.* 23 months (95% CI [0-46.6]) ; $p = 0.024$) and RO resections (median not reached *vs.* 9 months (95% CI [0-20.8]) ; $p = 0.017$).

Locoregional recurrence-free interval (LRFI)

Median LRFI was not reached at analysis. There were 6 local recurrences during the follow-up. LRFI rates at 2 and 5 years were 81.5% and 64.8%, respectively (Fig.

Table 1. — **Patient and tumor characteristics at baseline. %, percentages are calculated in relation to number of available data**

		All	No or incomplete remission	Complete remission	*p-value (Khi² or Fisher)*
Total		45	11	34	
Age					.430
	Median [Min-Max]	62 [11.2-83.4]	58.6 [18.5-83.4]	63.1 [11.2-82.5]	
Sex					
	Female	21 (47)	8 (73)	13(38)	.049
	Male	24 (53)	3 (27)	21 (62)	
Age > 40y					
	No	7 (16)	4 (36)	3 (9)	.050
	Yes	38 (84)	7 (64)	31 (91)	
Tumor size > 7cm					
	No	10 (25)	0	10 (32)	.081
	Yes	30 (75)	9 (100)	21 (68)	
Multifocal tumor					
	No	38 (86)	7 (64)	31 (94)	.027
	Yes	6 (14)	4 (36)	2 (6)	
Grade					
	I	4 (10)	0 (0)	4 (13)	.574
	II	15 (38)	4 (44)	11 (35)	
	III	21 (53)	5 (56)	16 (52)	
Lymphovascular invasion					
	No	40 (95)	8 (89)	32 (97)	.387
	Yes	2 (5)	1 (11)	1 (3)	
Surgery					
	No	4 (9)	3 (27)	1 (3)	.040
	Yes	41 (91)	8 (73)	33 (97)	
Surgical margins					
	R0	27 (82)	1 (33)	26 (87)	.078
	R1	6 (18)	2 (67)	4 (13)	
Adjuvant chemotherapy					
	No	39 (87)	9 (82)	30 (88)	.624
	Yes	6 (13)	2 (18)	4 (12)	
Neoadjuvant chemotherapy					
	No	43 (96)	11 (100)	32 (94)	.567
	Yes	2 (4)	0	2 (6)	
Radiotherapy					
	No	38 (86)	9 (90)	29 (85)	.585
	Yes	6 (14)	1 (10)	5 (15)	
Tumor site					
	Colon	10 (22)	1 (9)	9 (26)	.191
	Duodenum	3 (7)	2 (18)	1 (3)	
	Oesophagus	1 (2)	1 (9)	0	
	Rectum	7 (16)	2 (18)	5 (15)	
	Small intestine	18 (40)	4 (37)	14 (41)	
	Stomach	6 (13)	1 (9)	5 (15)	
Histological type					
	Leiomyosarcomas	24 (54)	4 (36)	20 (59)	.342
	Undifferentiated sarcomas	10 (22)	4 (36)	6 (18)	
	Other	11 (24)	3 (28)	8 (23)	

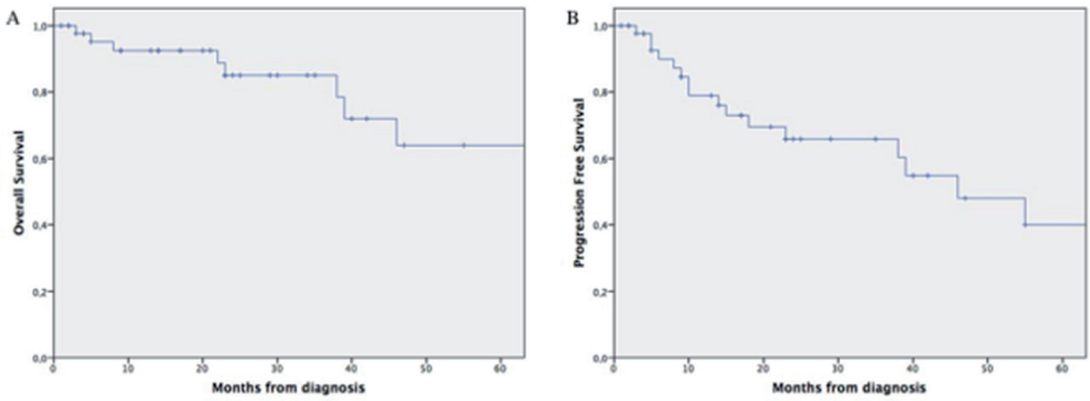

Figure 2. — A. Overall survival and B. Progression-free survival.

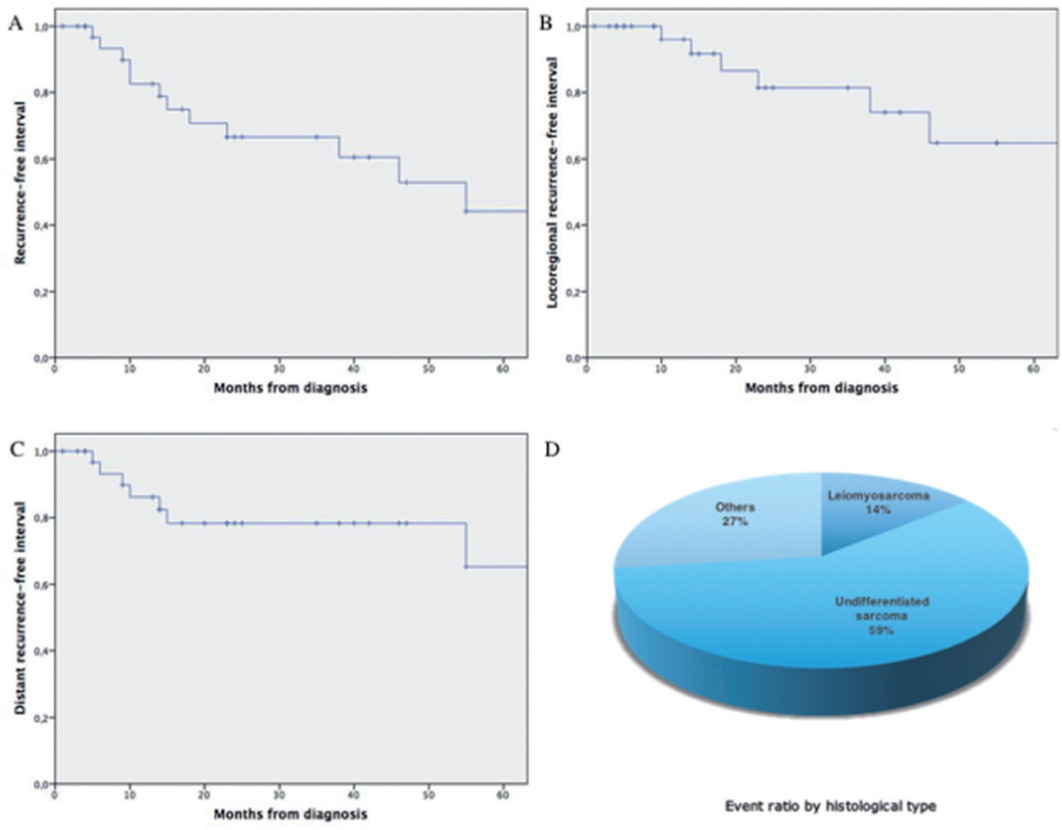

Figure 3. — A. Recurrence-free interval ; B. Locoregional recurrence-free interval ; C. Distant recurrence-free interval ; and D. Event ratio by histological type.

3B). Criteria associated with a better LRFI were female sex ($p = 0.049$), leiomyosarcoma histology (median not reached *vs.* 38 months (95% CI [8.9-67]) ; $p = 0.008$) and no adjacent organ invasion (median not reached *vs.* 18 months (95% CI [0-41.5]) ; $p = 0.02$).

Distant recurrence-free interval (DRFI)

Median DRFI was not reached at analysis. There were 7 distant events during the follow-up. DRFI rates at 2 and 5 years were 78.3% and 65.3%, respectively (Fig. 3C). Only R0 resections were associated with a better DRFI (83.7 *vs.* 9.6% 2 years DRFI; $p=0.05$).

Recurrence by histological type

Regarding histological subtypes, leiomyosarcomas (n = 20 ; 59%) and undifferentiated sarcomas (n = 6 ; 18%) were still predominant among patients in remission after primary treatment. Recurrence events occurred mainly in the undifferentiated sarcomas (Fig. 3D). Leiomyosarcomas were mainly located in the small intestine (n = 7 ; 35%). Median age at diagnosis was 63 years (range 19.5-82.3). There was no significant difference in the clinical features or in the treatment compared to the rest of the cohort. Five events occurred in 4 patients during the follow-up: 1 death, 1 local and 3 distant recurrences. Median DRFI was not reached in this subgroup at analysis. 2-year DRFI rate was 81.9% *vs.* 46.9% in the other histological types ($p = 0.024$). Most of the undifferentiated sarcomas were located in the small intestine (n = 5; 83%) and one (17%) in the stomach. Median age at diagnosis was 69.8 years (range 39-80.5). Compared to the rest of the cohort, no significant difference in clinical features or treatment was found. Seven events occurred in 5 patients during the follow-up : 2 deaths, 2 local and 3 distant recurrences. Median DRFI was 23 months (95% CI [5.8-40.2]) *vs.* unreached in the other histological types and 2-year estimated DRFI was 40% *vs.* 73.1% ($p = 0.025$).

Discussion

In this large, multicenter, retrospective cohort, we examined the clinical and pathological characteristics and outcomes of untreated localized sarcomas of the digestive tract, excluding GIST. Leiomyosarcomas and undifferentiated sarcomas were predominant, the former having better OS and PFS than the other histological subtypes while undifferentiated sarcoma had a worse prognosis than the other histological types. In one published series, the most frequent histological types for all soft tissue sarcomas excluding GIST were undifferentiated sarcoma (16%) and liposarcoma (15%) (7). In our series, complete remission was obtained in 75% patients. Complete remission was associated with male sex, age over 40 and monofocal tumor in univariate analysis. Considering the patients in complete remission, female sex and leiomyosarcoma histology were associated with a better RFI and LRFI, microscopically safe resection margins were associated with better RFI and DRFI, and tumor invasion of adjacent organs was associated with a worse LRFI. Considering the number of cases by histological type, recurrences occurred mainly in undifferentiated sarcomas. On the other hand, leiomyosarcomas seemed to have a better prognosis without any significant difference in baseline characteristics or treatment modalities.

To our knowledge, there has not been any other published series reporting clinico-pathologic characteristics and clinical outcomes in localized sarcomas of the digestive tract, excluding GIST, probably owing to their low incidence and heterogeneous presentation. Kevin C. Conlon *et al*, reported (8) a retrospective study that examined 38 cases of sarcomas of the gastrointestinal tract excluding GISTs, recruited between July 1982 and December 1991. These patients represented 2% of all STM diagnosed during this period at Memorial Sloan Kettering Cancer Center in New York. Disease was localized to the primary site in only 81% of cases (n = 30). Thirty-five (92.1%) of 38 tumors were leiomyosarcomas and the most common site was the stomach (20 cases). The actuarial OS was 28% at 5 years, with a median follow-up of 26 months vs. 63.9% in our study. This could be due to the considerable changes that have taken place in the therapeutic management of sarcoma since 1995, both in terms of surgical techniques and complementary treatments such as chemotherapy or radiotherapy, when feasible. Inaugural weight loss ($p = 0.02$) and algic manifestations leading to diagnosis ($p = 0.05$) were factors of poor prognosis. Histological grade ($p = 0.0002$) and complete resection had a significant impact on OS. Resection of adjacent organs or tumor size did not affect OS as soon as the primary tumor was resected completely ($p = 0.422$). Age, ethnic background, gender, mode of diagnosis (emergency or programmed surgery), size of the tumor and completion of adjuvant treatment were not significant prognostic factors.

Our study has some major limitations consisting mainly in its retrospective design with potential selection bias and lack of standardization in treatment strategies, owing to the lack of information about signs and symptoms on presentation. However, it has several strengths such as the large size of the multicenter cohort from which the study population was extracted and the central histological review in a referral center for each case. In addition, while this study was not a randomized clinical trial with selected patients under defined protocol care, our population was more likely to be representative of a "real-life" cohort, with several patients not receiving the complete treatment or ideal care because of their own choice, advanced age or comorbidities. It is very unlikely that a prospective trial will be conducted in the future in this population, which reinforces the interest of the present study.

In conclusion, localized sarcomas of the digestive tract (excluding GISTs) are a rare, heterogeneous and poorly known entity. Survival was better than in previous series. Complete surgery seems to be crucial regardless of tumor localization. Given the major prognostic differences by histological subtype, a centralized histological review in referral centers is of major interest so that patient outcomes are clearly understood. The prognosis of undifferentiated sarcomas would likely benefit from complementary treatments. Finally, it would be interesting to know the endoscopic aspect of these tumors in order to establish whether the different histological subtypes have different characteristics. This can only be done through a prospective study, which would require complex collaboration.

Conflict of interest

Authors have nothing to disclose.

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