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Research Article

Different Quality of Treatment in Retroperitoneal Sarcomas (RPS) According to Hospital-Case Volume and Surgeon-Case Volume: A Retrospective Regional Analysis in Italy

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Abstract

Background: Retroperitoneal Sarcomas (RPS) should be surgically managed in specialized sarcoma centers. However, it is not clearly demonstrated if clinical outcome is more influenced by Center Case Volume (CCV) or by Surgeon Case Volume (SCV). The aim of this study is to retrospectively explore the relationship between CCV and SCV and the quality of surgery in a wide region of Northern Italy.

Materials and Methods: We retrospectively collected data about patients surgically treated for RPSs in 22 different hospitals from 2006 to 2011, dividing them in two hospital groups according to sarcoma clinical activity volume (HCV, High Case Volume or LCV, Low Case Volume Hospitals). The HCV group (>100 sarcomas observed per year) included a comprehensive cancer center (HVCCC) with a high sarcoma SCV, and a Tertiary Academic hospital (HVTCA) with multiple surgeon teams and a low sarcoma SCV. All other hospitals were included in the LCV group (< 100 sarcomas observed per year).

Results: data regarding 138 patients were collected. LCV hospitals were excluded from the analysis as prognostic data were frequently not available. Overall survival was evaluated with a multivariate Cox model. Among HCV hospitals 72% of cases had R0/R1 margins, with a more favorable distribution of R0/R1 versus R2 in HVCCC compared to HVTCA. According to multivariate Cox analysis, no covariates were significantly correlated with survival outcomes.

Conclusions: In HCV hospitals, sarcoma SCV may significantly influence RPS treatment quality. In low-volume centers surgical reports can often miss important prognostic issues and surgical quality is generally poor.

Keywords: Retroperitoneal sarcomas; Multidisciplinary management; Hospital case volume; Surgeon case volume; Quality of surgery; Retrospective analysis

Introduction

Retroperitoneal Sarcomas (RPS) account for 10-15% of Soft Tissue Sarcomas (STS) with an expected annual incidence of nearly 1500 cases in Europe and an expected 5-year Overall Survival (OS) of 30-35% [1]. Histopathological analysis can reveal multiple histotypes with liposarcoma, leiomyosarcoma and pleomorphic undifferentiated sarcoma as the most common types [2].

Radical surgery is the only curative treatment for localized RPS (L-RPS) [3], while in the advanced setting (relapsing or metastatic RPS) surgical treatments are mostly palliative.

In Soft Tissue Sarcomas (STS) radical surgery needs to respect anatomic compartments; however, the peculiar anatomy of the retroperitoneum makes it difficult to identify well-defined compartments and RPS often involve abdominal or pelvic organs whereof resection could be technically difficult or unacceptable for quality of life. Another key aspect of the management of RPS is obtaining a pre-surgical histological diagnosis to assess if preoperative chemotherapy or radiotherapy could be worthwhile (especially in responsive histotypes). Achieving complete resection with microscopically negative resection margins provides the best chance for local control. Of course, a wide margin per se may not be enough to guarantee an improved prognosis especially in specific histotype (e.g. leiomyosarcoma) thus making it crucial to balance between wider excision and functional outcome [4].

Considering these aspects, available guidelines and consensus-papers state that, as a complex and rare disease, every case of RPS should be referred to a specialized sarcoma center and managed by a multidisciplinary team [5-7].

Some retrospective data show that the management of L-RPS in sarcoma-specialized centers is associated with a lower loco-regional relapse rate and a 5-year OS of nearly 60-65% [8,9] and that high-volume centers perform surgery more adherently to clinical STS guidelines than low-volume ones [10,11].

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In real life, up to 63% of STS in UK are referred to non-specialized centers [12]; up to 50% of non-oncology committed surgeons perform extremity soft tissue sarcoma resections in California [13]. In a recent survey of the German Interdisciplinary Sarcoma Group [14] regarding the care of retroperitoneal sarcomas, heterogeneous diagnostic and therapeutic strategies were found. Analyzing university medical centers plus those ones treating more than 10 RPS per year compared to centers following less than 10 RPS per year, relevant differences were identified regarding tumor biopsy policy, resection strategies and multimodal therapies suggesting the need for dedicated RPS education programs and centralized registration for RPS treatment.

However, it is not clearly demonstrated if for STS, and specifically for RPS, clinical outcome is more influenced by Center Case Volume (CCV) or by Surgeon Case Volume (SCV). Published retroperitoneal sarcoma series are mostly collected from high volume centers, in which the multidisciplinary aspect is most relevant rather than the surgeon's caseload.

NICE guidelines state that a surgeon with specific expertise in these tumors, who is a core member of the Multidisciplinary Team (MDT), is needed within a reference center; they also consider the number of new cases per year as an important quality evaluation item for sarcoma multidisciplinary teams. A sarcoma MDT should be expected to manage at least 100 new STS patients per year, and this caseload should be based either in a single hospital or in several geographically close and closely affiliated hospitals, which would constitute a sarcoma treatment network [15].

Due to the rarity of these diseases, it is difficult for a general surgeon to reach an adequate case volume. The only paper dealing with the problem of adequate surgical volumes in STS proposed a > 5 sarcoma surgeries/year cut off, after an analysis of 4205 STS cases registered in the Florida Cancer Data System (FCDS) in which medical facilities above the 67th percentile for volume were defined as high-volume centers [16].

The aim of this study is to retrospectively explore the relationship between the hospital or surgeon case volume and the quality of surgery in a region of Northern Italy.

Materials and Methods

We retrospectively collected data concerning 2 regions of northern Italy, Piedmont and Aosta Valley (with a total amount of 4.5 million of inhabitants), to identify RPS patients operated during the period from 2006 to 2011 in order to analyze OS, care center characteristics (according to high or low CCV and SCV) and quality of surgical treatment. Data collection was authorized by a partnership between the Department «Rete Oncologica del Piemonte e della Valle d'Aosta» (Piedmont and Aosta Valley Oncologic Network) and Italian Pathologist Association (SIAPEC) stipulated in June 2012; all data were recorded anonymously respecting Italian privacy rules.

Data of histopathological reports from January 2006 to December 2011 were collected from local databases of 22 different hospitals. According to the type of electronic database available in every single hospital, site-specific search strings were prepared using keywords able to describe the site and the morphology (i.e. "retroperitoneum" and/or "sarcoma") and SNOMED codes used for sarcomas morphology [17].

All extracted cases were screened by a skilled medical oncologist and collected in an encrypted database, which contained clinical and histopathological data, with particular attention to ESMO guidelines main prognostic items such as tumor size, grading, surgical margins (according to the R0, 1 and 2 ranking), preoperative biopsy, multifocality, tumor integrity, and the presence of distant metastases at the time of diagnosis.

In our study patients data retrieved from different hospitals were split in 2 groups according to their yearly sarcoma caseload, adopting the 100 cases/year cut-off rule suggested by NICE (15).

In the "high volume" group two institutions are included:

- "Candiolo Cancer Center, a High Volume Comprehensive Cancer Center (HVCCC) with nearly 150 STS cases observed per year
- "Città della Salute e della Scienza" San Giovanni Battista hospital, a high volume tertiary care academic hospital (HVTCA) with more than 100 STS cases observed per year.

In the "low volume" group all other hospitals were included (low volume secondary care hospitals, LVSCH).

In this series three different approaches to RPS are represented:

- HVCCC, a high-volume cancer center with a sarcoma-committed surgical team (high CCV and high SCV) and a regular RPS-Multidisciplinary Board (RMB)
- HVTCA, a high-volume tertiary care academic hospital without a sarcoma-committed surgical team (high CCV and low SCV) and without a formalized RMB;
- LVSCH, a group of low volume hospitals (low CCV and SCV) without a formalized RMB.

Missing clinical informations concerning the "high volume" group were sorted from the institutional internal electronic chart database of each institution.

Missing data about the patients in charge to LVSCH were not obtained, due to the absence of a reliable database or, in case of an existing one, to access restrictions for external investigators.

Statistical analysis

Data were analyzed with SAS system 9.2 software.

The crude and adjusted hazard ratios were calculated according to hospital, patient's age, tumor size, grading, recurrent or primitive tumor. Two logistic regression models were adopted: for tumor integrity and for surgical margins (confidence limits 95%).

Follow-up was available for 118 patients, according to the regional database.

The Kaplan Meier survival curve for primary/recurrent RPS was calculated on 101 patients. The Kaplan Meier survival curve according to surgical margins was built with the high HCV hospitals data, and is based on 52 patients.

Overall survival was evaluated with a multivariate Cox model,

Table 1: Rate of missing data and distribution in low volume centers.

	not available	Not available in LVSCH
Primitive/recurrent	19,5%	100%
M0/M1	48%	100%
FNCLCC grading	42%	80%
tumor diameter	52%	97%
Preoperative biopsy	49%	96%
surgical margins	55%	98,5%
tumor integrity	53%	98%

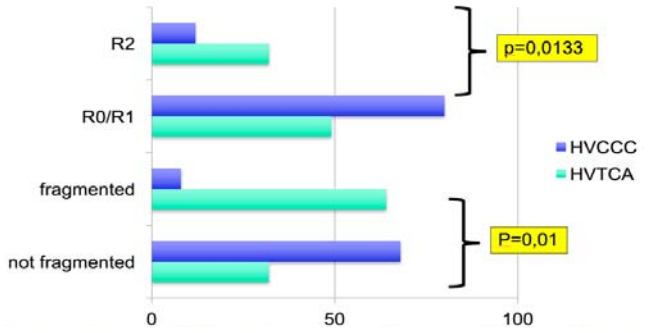

Figure 1: Analysis of margin involvement and specimen fragmentation according to the hospital of treatment (HVCCC *vs*. HVTCA). P values are derived from Chi-square test.

stratified for age, grading, hospital, surgical margins, histologic type, tumor size, primary/recurrent, and tumor integrity.

Results

Data from 22 hospitals were available: 138 patients (55% males and 45% females) were identified with diagnosis of RPS from 2006 to 2011.

According to care center volume 47 cases (34.1%) were treated in HVTCA, 25 (18.1%) in HVCCC: 66 cases (47.8%) were treated in LVSCH.

As regards this latter group of patients, the lack of essential information impaired any statistical analysis. In particular, no useful information were available concerning tumor diameters, preoperative biopsy, margins evaluation, FNLCLCC grading and presence of synchronous metastasis (Table 1).

Seventeen different histotypes were observed. The most frequent was liposarcoma (45.6%), followed by leiomyosarcoma (19.5%).

The tumor was primitive in 56.5% and recurrent in 24%: this information was not available in 19.5% of cases,. In HVCCC primaries were 56% and recurrences 44%; in HVTCA 68% and 32%. (Chi Squared test, p = 0, 30).

Seventeen percent of patients had synchronous metastases and 34% were M0; in 48% of patients these data were not available. The rate of metastatic disease in HVTCA and HVCCC patients was 34 and 28% respectively.

According to FNCLCC grading, 15% of tumors were G1, 15% were G2 and 27% G3. In 42% of cases, this information was not recorded.

Table 2: Logistic regression model for surgical margins (R0/1 *vs.* R2) (HVCCC *vs.* HVTCA).

COVARIATES	Rough Effects	P	IC 95%	Adjusted Effects	P	IC 95%
HTVCC	--	--	--	--	--	--
HTVCA	5.262	0.019	1.311-21.115	8.335	0.031	1.220-57.242
Liposarcoma	--	--	--	--	--	--
Leiomyosarcoma	1.094	0.906	0.248-4.829	1.193	0.839	0.218-6.543
others	1.176	0.855	0.206-6.731	0.47	0.562	0.037-6.034
Age	0.97	0.339	0.912-1.032	0.973	0.482	0.903-1.049
primary	--	--	--	--	--	--
recurrent	1.45	0.549	0.430-4.889	3.252	0.161	0.626-16.897
< 10 cm	--	--	--	--	--	--
> 10 cm	1.107	0.883	0.285-4.297	0.808	0.81	0.141-4.617
G1	--	--	--	--	--	--
G2/G3	0.288	0.08	0.071-1.159	0.365	0.349	0.045-2.999
unknown	3.718	0.237	0.422-32.759	1.687	0.736	0.080-35.384

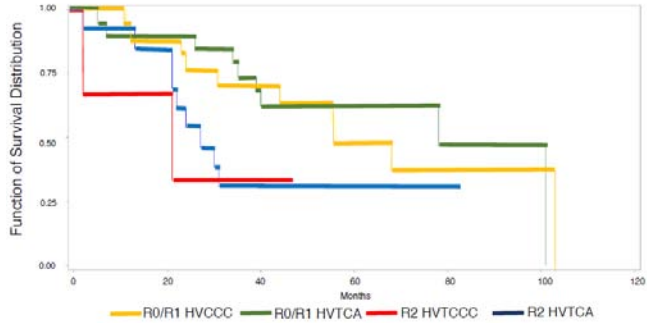

Figure 2: Kaplan-Meyer curves according with the status of surgical margins (R0/R1 *vs.* R2;) patients from HVCCC versus patients from HVTCA.

The subdivision of grades G1/G2-3 in HVCCC and HVTCA was 28/52% and 15/68% (Chi Squared test, p =0.91), respectively.

Tumor diameter was smaller than 10 cm in 13% of cases (30% for HVTCA and 12% for HVCCC), greater than 10 cm in 35% (68% for HVTCA and 60% for HVCCC) and unknown in 52%; (Chi Squared test, p =0,2622) .

A preoperative biopsy was performed in 19% of patients: this information was not available in 49% of cases.

Surgical resections were classified as macroscopically complete (R0 or R1) or not (R2) [18]. Thirty-two percent of RPS had a R0/R1 resection, 13% had R2 resection. In 55% of cases the status of surgical margins was not recorded. In 72% of cumulative HVCCC and HVTCA series, free or marginally involved margins (R0 or R1) were observed. In HVCCC group the distribution R0/R1 *vs.* R2 was 80% and 12%; in HVTCA, 49% and 32% (Chi Squared test, p =0.0133; Figure 1).

Tumor was fragmented in 23% of cases: these data were not available in 53 patients. In HVCCC group the rate of fragmented/not fragmented specimens was 24% and 68%, and in HVTCA, 64% and 32% (Chi Squared test, p=0.01, Figure 1), respectively.

Table 3: Survival analysis according to cox model.

Covariates	Rough HR	P	IC 95%	HR s	P	IC 95%
HTVCC	1	--	--	1	--	--
HTVCA	0.915	0.802	0.459-1.824	0.79	0.548	0.367-1.703
Liposarcoma	1	--	--	1	--	--
Leyomiosarcoma	0.86	0.75	0.340-2.176	1.06	0.909	0.392-2.865
others	0.738	0.441	0.341-1.597	0.76	0.526	0.329-1.767
Age	1.03	0.146	0.990-1.071	1.04	0.077	0.996-1.081
recurrent	1	--	--	1	--	--
primary	0.923	0.814	0.472-1.804	0.8	0.566	0.375-1.708
< 10cm	1	--	--			
> 10cm	2.006	0.103	0.869-4.629	2.02	0.121	0.831-4.928
G 1	1	--	--	1	--	--
G 2	1.391	0.515	0.515-3.752	1.93	0.244	0.640-5.790
G 3	1.629	0.352	0.583-4.550	2.17	0.189	0.683-6.900

We compared HVTCA and HVCCC groups with the Chi squared test for grading, surgical margins, tumor size and tumor integrity. In both logistic regression models concerning tumor integrity and surgical margins (Table 2), only the "care center" item demonstrated a statistically significant correlation (i.e. HVCCC versus HVTCA). (p= 0.03, adjusted effects)

Overall Survival (OS) was analyzed by a multivariate Cox analysis. None of the covariates (hospital, age, tumor size, grading, primary or recurrent tumor) was significantly correlated with survival outcomes (Table 3); then OS was stratified according to the quality of surgical margins recorded in the two high CCV centers, but no differences were observed (the care center being equal, p> 0,05, Figure 2).

Discussion

The outcome of surgical treatment of many common tumors (as for example rectal cancer, breast cancer, lung cancer, prostate cancer, head and neck cancers and esophageal cancer) are clearly influenced by both Center Case Volume (CCV) and Surgeon Case Volume (SCV) [19,20].

In STS, several studies state that HCV hospital may assure higher survival rate [12,16].

There are data concerning RPS which show that patients treated in sarcoma reference centers can achieve better oncological outcomes [8,9].

The management of soft tissue sarcomas requires integrated care at a referral center, as suggested by existing guidelines and consensus statements. Diagnosis of the primary lesion, distant metastasis, or subsequent local recurrence requires the use of advanced imaging as well as the expertise of appropriately trained teams. Experts involved in soft tissue sarcoma care suggest treatment with respect to using, dosing, and timing of radiation and chemotherapy tailored for every individual patient with a soft tissue sarcoma [5,21].

Unfortunately, a large proportion of patients with soft tissue sarcoma may be subject to an initial incidental and suboptimal surgery, more often when the multidisciplinary team is not available, which may result in the need of further subsequent more extensive surgery and postoperative radio or chemotherapy. Factors such as treatment delay and provision of optimal treatment can explain about a third of the observed differences in cancer quality of care, while clinical guidelines, professional training and quality control measures, may be responsible for another quarter of the outcome differences [22].

Surgery of RPS, especially for wide re-excision after unplanned primary excision of a mass, requires specific multidisciplinary teamwork [23,24].

However, it is not clear if clinical outcome is more influenced by the CCV or by SCV.

In order to evaluate this aspect, in this study we compared low volume activity hospitals (LVSCH) and hospitals with high CCV but with different SCV: multiple surgical teams with different SCV (HVTCA), or a dedicated surgical team with a high SCV volume activity (HVCCC). Moreover, in HVCCC a multidisciplinary board discussed weekly every case of RPS, while in HVTCA a RMB was settled only in November 2016.

Globally, we collected data from 22 hospitals, of which 20 (90%) treated less than 5 cases per year. Forty-eight percent of patients were treated in low volume hospitals (LVSCH).

The epidemiological data of this series, collected across two Italian regions by using pathological reports, are similar to those of the available literature regarding age, sex and histotypes [9]. The low quality of collected data mirrors the incidental character of this type of surgery.

Due to the paucity of prognostic data in the LVSCH group, only the two high HCV institutions were compared for outcomes and surgical quality.

The two groups were homogeneous for age, histotypes distribution, tumor size, primary/recurrent rate, grading and occurrence of preoperative biopsies.

In available literature, the status of margin is often grouped in grossly negative (R0 and R1) versus grossly positive (R2) with a well-defined prognostic value [6,25-29].

Regarding retroperitoneal sarcomas, the absence of a real compartment or the possibility of a wide excision makes mandatory, in a retrospective data collection, to group the surgical outcomes in macroscopically complete or incomplete (R0/1 *vs*. R2) [27,28].

The multivariate analysis confirmed that, within high CCV centers, the one with a dedicated surgical team and a RMB (HVCCC) had a better quality of margins and a higher rate of tumor integrity compared with the hospital without a dedicated team and without a RMB (Figure 1).

Probably due to the limited number of cases (52 for this analysis), involved surgical margins, independently from the caring institution, did not produce statistically different survival data; at the same time, no difference was shown in OS between HVTCA and HVCCC in cases in which surgical margins quality was the same (Figure 2).

The COX regression model analysis showed a nearly significant improved survival linked to the case-volume of the treating institution

and to whether the lesion was primitive or not (Table 3).

We can suppose that the lower quality of surgery due to less experienced surgical teams and the absence of a dedicated multidisciplinary board in HVTCA could have influenced the overall survival outcomes. In similar French studies R2 resection or local relapse rates were significantly related to tumor location, surgeon specialty and to the presence/absence of a multidisciplinary team [8,9].

Although a scenario already described in literature, important limitations of this study are the retrospective nature, based on histopathological reports, the omission of non-surgically treated patients, the retrieval of missing data from different databases and the absence of clinical history and follow-up information, particularly about disease-relapse, in patients treated in LVSCH.

In conclusion, outside reference or tertiary care centers, the quality of RPS management may be lower because the relevance of both tumor integrity and surgical margin quality are not completely understood and therefore, documented.

Among centers with High-Case Volume (HCV), the multivariate analysis identified that Surgeon's Activity Volume (SCV) and a dedicated multidisciplinary board may significantly influence the quality of treatment.

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