

Management of Recurrent or Metastatic Retroperitoneal Soft-Tissue Sarcomas

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Rezumat

Managementul sarcoamelor țesuturilor moi retroperitoneale recurente sau metastatice

Sarcoamele de țesut moale retroperitoneal rămân o problemă terapeutică serioasă.

Scopul prezentului studiu este de a defini strategia terapeutică optimă la pacienții cu sarcoame de țesut moale retroperitoneal recurente sau metastatice.

Material și metode: S-a efectuat un studiu retrospectiv. În perioada 2001-2013, 89 de pacienți cu sarcoame ale țesutului moale retroperitoneal au fost tratați chirurgical în cadrul Spitalului Universitar "Tsaritsa Yoanna - ISUL" și a Spitalului Specializat pe Tratament Oncologic Activ din Sofia. Datele clinicopatologice au fost procesate cu ajutorul programului SPSS-19.

Rezultate: Perioada medie de recurență a fost de 23 de luni pentru primul, respectiv 13 luni pentru cel de-al doilea episod. Peste 40% dintre pacienții în studiu au fost supuși la mai mult de o operație ca urmare a recurențelor. Capacitatea de extirpare radicală a tumorii a scăzut cu fiecare recurență succesivă. Supraviețuirea la 5 ani a fost de 60% pentru pacienții cu rezecție primară radicală combinată, față de 28% la cei cu rezecție parțială. În prezența leziunilor metastatice supraviețuirea la 3 ani a fost de doar 22%.

Concluzii: Recurențele locale, prezența metastazelor la distanță

și posibilitatea de efectuare a extirpării radicale constituie factorii prognostici pe termen lung ai acestei afecțiuni.

Cuvinte cheie: recurent local, metastatic, sarcoame ale țesutului moale retroperitoneal, rezecție, radioterapie

Abstract

Retroperitoneal soft-tissue sarcomas remain a serious therapeutic problem.

The *aim* of the study is to define the optimal treatment strategy of patients with locally recurrent or metastatic retroperitoneal soft-tissue sarcomas.

Material and methods: A retrospective study was performed. Between 2001 and 2013, 89 patients with retroperitoneal soft-tissue sarcomas were surgically treated in the University Hospital "Queen Joanna - ISUL" and the Specialized Hospital for Active Treatment in Oncology - Sofia. Clinicopathological data were investigated with SPSS-19.

Results: The mean time of onset of the first and second relapse of sarcomas was 23 and 13 months, respectively. Over 40% of the studied patients underwent more than one operation because of recurrence. Ability of radical extirpation of the tumour decreased with each subsequent relapse. The 5-year survival rate was 60% for patients with primary combined radical resection versus 28% for patients with partial resection. In the presence of metastatic lesions the 3-year survival rate was only 22%.

Conclusion: Local recurrences, the presence of distant metastases and the ability of radical extirpation are the main long-term prognostic factors.

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Key words: locally recurrent, metastatic, retroperitoneal soft-tissue sarcomas, resection, radiotherapy

Introduction

Retroperitoneal soft-tissue sarcomas remain a serious therapeutic problem because recurrent disease occurs in 40-80% of cases even after a radical resection. (1) More than 75% of patients' deaths are the result of a relapse. (1,2) Sarcomas metastasize mainly by blood. Metastases in lymph nodes are extremely rare (<5%). Local recurrence or distant dissemination of the process significantly decreases the survival. Another factor that shortens the life of patients is the presence of residual tumor mass (R1). For now, surgical removal of the tumor is the method of choice in treatment, but it alone is not sufficient to significantly prolong life. In advanced cases radiotherapy or chemotherapy should be considered. The AIM of the study is to define the optimal treatment strategy for patients with locally recurrent or metastatic retroperitoneal soft-tissue sarcomas.

Material and Methods

The investigation of the problem related to management of recurrent or metastatic disease is part of a retrospective study of retroperitoneal tumors which includes 115 patients, operated at the University Hospital "Queen Joanna - ISUL" and Specialized Hospital for Active Treatment in Oncology -

Sofia over the period 2001-2013. There were 89 cases with retroperitoneal soft-tissue sarcomas- 45 males and 44 females (sex ratio 1.02:1). The median age in the group was 55 years and 4 months. In seven patients postoperative radiotherapy was applied and preoperative radiotherapy was used in 5 cases. In recent years, we apply preoperative radiotherapy for large tumors, often with involvement of adjacent organs and vessels in order to reduce the possible subsequent recurrences. We have no great experience with chemotherapy.

Clinicopathological data were analysed with the software package SPSS-19. Due to the frequent recurrence of retroperitoneal sarcomas we processed statistically the recurrence rate against the total number of tumors. The National Cancer registry provided full information, being the only system that allows insight into the history of the disease and follow-up of the patients.

Results

Table 1 shows the cases with postoperative recurrence of soft tissue sarcomas. For the period 2001-2013, 37 cases were identified (41.6%) of the total number of surgically treated patients with sarcomas. Additional distribution of the patients was performed according to the histological subtype of tumor.

We divided the cases with recurrences according to the time to onset of the first and second relapse after macroscopically radical surgery. Additional distribution was performed according to histological subtype. Results are presented in Table 2. We do not have any data for the time to onset of the second relapse in the case of patients with

Table 1. Histological subtypes

Histological subtype	Total number	Number of patients with recurrence	% of relapse to the total number of patients with soft-tissue sarcomas
Liposarcoma	56	19	21.3
Leyomyosarcoma	10	6	6.7
Fibrosarcoma	8	4	4.5
Histiocytoma	6	3	3.4
Rhabdomyosarcoma	4	2	2.2
Fibromyxosarcoma	4	2	2.2
Myofibrosarcoma	1	1	1.1

Table 2. Time to onset of relapse

Histological subtype	Number of patients with relapse	Mean time to onset of I relapse (in months)	Mean time to onset of II relapse (in months)
Liposarcoma	19	19	14
Leiomyosarcoma	6	25	10
Leiomyosarcoma	4	39	12
Histiocytoma	3	13	6
Rhabdomyosarcoma	2	12	No data
Fibromyxosarcoma	2	36	26
Myofibrosarcoma	1	24	3

Table 3. Number of performed operations per patient with retroperitoneal soft-tissue sarcoma

Number of performed operations per patient with retroperitoneal soft-tissue sarcoma	Number	% of total number of patients with retroperitoneal soft-tissue sarcoma
One operation	53	59.6
2 operations	21	23.6
3 operations	12	13.5
> 3 operations	3	3.4
Total	89	100

rhabdomyosarcoma because these cases underwent primary radical surgery in the clinic without recurrence or they had already undergone several surgical interventions for which there was no documentation.

Tendency towards recurrence of soft tissue sarcomas is confirmed by the analysis on the number of performed operations per one patient with this type of tumor (Table 3).

40.5% of studied patients underwent more than one surgery due to recurrence of the process. On the other hand, the number of operations and the number of operated patients were inversely proportional. Indirectly, these results are related to the fact that the ability to perform extirpation decreases with each subsequent relapse. Achievement of radical extirpation is essential to improve long-term results of surgical treatment. Confirmation of this is Fig. 1 presenting the cumulative survival of the patients with retroperitoneal soft tissue sarcomas according to the type of the intervention. Five-year survival rate was 60% for patients with combined radical surgery, 53% for patients with radical extirpation of the tumor itself versus only 28% for patients with partial resection.

Regarding the localization of metastases in our study, they were most common in the liver (in 9.5% of cases) and lymphatic metastases were registered in only 1 case (Table 4). In 5 patients removal of the metastatic lesions together with the tumor was carried out. In three patients a secondary liver resection was performed.

The Kaplan-Meier analysis of survival for patients surgically treated for retroperitoneal soft tissue sarcomas with distant metastases is presented in Fig. 2.

In this study, neoadjuvant radiotherapy was conducted only in 5 patients. Reduction in tumor size was achieved in two of them, followed by radical surgery. In 7 patients

Table 4. Localization of metastases in patients with retroperitoneal soft-tissue sarcoma

Localization of metastases	Sarcomas	Total %
Liver	8	9.0
Peritoneum	6	6.7
Abdominal wall	2	2.2
Lymph nodes/omentum	1	1.1
Total	17	19.1

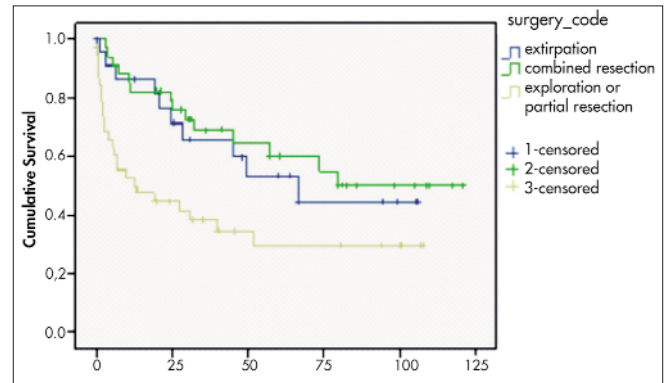


Figure 1. Survival of the patients with retroperitoneal soft tissue sarcomas according to the type of intervention

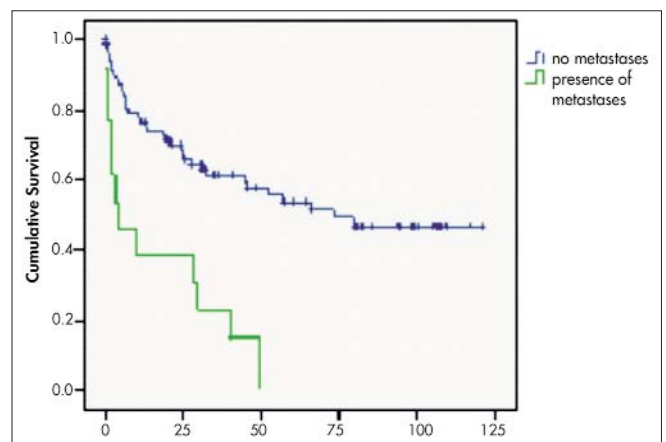


Figure 2. Survival of the patients with retroperitoneal soft-tissue sarcoma according to the presence of distant metastases

adjuvant radiotherapy was carried out, but four of them were operated non-radically. For the latter ones there was no improvement of survival. The other three had undergone tumor extirpation with doubtful resection margins. In one of the patients a separation of the formation of vascular structures and plastic vessels was required. In these cases the tumor was myxoid liposarcoma and a combination with chemotherapeutic agent – Doxorubicin was applied. Relapse was established about 13 months later. Then, the case was considered as advanced and was directed to continue chemotherapy and radiotherapy, and then was lost from observation. Our experience with chemotherapy in patients surgically treated for retroperitoneal soft tissue sarcomas is limited. Only three patients were included in programs with Doxorubicin 75 mg/m². A course consisted of 6 cycles over a period of three weeks. One patient has been already described as successful. The other two patients developed complications from treatment.

Discussion

Retroperitoneal sarcomas represent approximately 80-85% of all primary retroperitoneal tumors. They occur at any age (average 50) and with approximately equal ratio in men and women.

Soft tissue sarcomas are characterized by local recurrence in 70% of cases at 10-year follow-up. (3,4) Presence of metastases or local recurrence have been proven as prognostic factors associated with decreased survival rate. Local recurrence is the leading cause of death in patients with retroperitoneal soft tissue sarcomas. (5,6,7,8,9) The method of choice for local recurrence is surgical treatment, and radical removal is a major factor influencing long-term results. (2) The treatment goal should be resection with macroscopically negative borders even if adjacent tissues and organs need to be removed. Liberal en bloc resections preserving the integrity of the tumor are considered when there are risky areas of residual tumor emboli. (10,11) Such fears are based on the theory that intra-abdominal tumor emboli are frequent at the time of primary surgery, and that these emboli are released at resection to become entrapped in fibrinous material along narrow resection margins. (12) The complex cytokine and protease cascades involved in wound healing may further contribute to establishment of tumor emboli diffusely in the retroperitoneal and peritoneal space. Respectively, the risk of tumor dissemination significantly increases with each subsequent operation (12) which confirms the need for aggressive surgery of local recurrence. (1,3,13) Early diagnosis determines the ability of radical extirpation in the most cases. (8) Potter et al. (1985) reported that 80% of recurrences occur within 5 years. (14) According to other authors the frequency of relapses is greatest in the first two years that as we observed too. (7) The ability of radical surgery decreases with each subsequent relapse. (1,9) According to our research the median time to onset of the first and second relapse calculated in months was 23 and 13 months, respectively. The analysis showed that the most rapid relapse was observed in cases of rhabdomyosarcoma - 12 months after surgery. Liposarcoma also recur relatively quickly - 19 months after the first operation, and 14 months after second. These data are the results of different biological behaviours, respectively of the aggressiveness of different histologic variants. In any case, regardless of histological subtype, time to onset of the second and each subsequent relapse is reduced. Several studies have demonstrated the influence of histological subtype and involvement of the adjacent tissues as important prognostic factors. (1,10,15,16,17,18,19) Liposarcomas are the most prevalent histologic subtype and they are associated with a favorable prognosis. In most studies the patients were divided into two groups - liposarcoma and others, but in this manner the specific influence of each histologic subtype cannot be evaluated. EA Perez et al. (2007) found that leiomyosarcoma and malignant fibrous histiocytomas were associated with poor prognosis as compared with liposarcoma. (18) A. Gronchi et al. (2009), however, separately analysed liposarcoma, leiomyosarcoma, fibrosarcoma, malignant tumors of peripheral nerve sheaths and found a poor prognosis for liposarcoma compared with leiomyosarcoma. (11) S. Bonvalot et al. (2009) presented in separate groups well-differentiated liposarcoma, other liposarcoma, leiomyosarcoma and malignant fibrous histiocytoma and found that well-differentiated liposarcoma had the most favorable prognosis. (10) It is believed that rhabdomyosarcoma and hemangiosarcoma are associated with a worse prognosis compared with lipo-

sarcoma. (20) Metastasis of soft tissue sarcoma is relatively infrequent. (7) Sarcomas metastasize mainly by blood (19%). Metastases in lymph nodes are extremely rare - in our study they were observed in 1.12% of patients. Because of this, prophylactic lymph node dissection is not recommended. Presence of distant metastases and grading, presented as M- and G- in AJCC-system are significant predictors of survival according to several studies. (1,10,11,16,17,20,21,22) In cases with metastatic disease survival decreases dramatically (9), which was also confirmed by the results of our study. Pulmonary metastases from soft-tissue sarcoma are associated with median survival of 6 to 12 months. (23,24) Several reports have shown that resection of even multiple metastases is associated with prolonged survival. (25,26,27,28) The reported 5-year survival was 25-37%. (25,26,28) In our study the observed 3-year survival of patients with metastases was only 22%, but only in rare cases survival of 50 months is achieved. The presence of liver metastases was associated with a significantly worse prognosis. Despite this, it was reported that the median survival was 30 months for patients who had hepatic resections compared with 11 months for those who did not. (29) Peritoneal metastases are a poor prognostic factor and unfortunately, they cannot be treated surgically. Achieving radical extirpation of the tumor is an undisputed prognostic factor associated with improved long-term results. (1,10,15,20,21,22) According to the literature, the 5-year survival rate varies between 43 and 65%. (1,11,15,20,21) In our study the 5-year survival was 60% for patients with combined radical surgery and 53% for patients with extirpation of the tumor. However, surgery is not sufficient as the only therapeutic method, which is confirmed by the high relapse rate and relatively low 5-year survival after radical surgery. (30,31) In this regard the role of radiotherapy and chemotherapy in the approach to patients with retroperitoneal soft tissue sarcomas has been explored. The role of radiotherapy is considered useful in soft-tissue sarcomas and is a standard practice in their treatment. (2,30,32,33) However, radiation therapy is more problematic in the management of retroperitoneal sarcomas because the adjacent organs and tissues often present low radiation tolerance. Increasing the dose improves the local control but significantly increases its toxicity. (7,34) In recent years, advantages of the combination of preoperative, intraoperative and postoperative radiotherapy in different versions were observed. Several studies reported improved local control with adjuvant radiotherapy. (3,6,10,15,17,29,34,35) Others demonstrated the role of preoperative and intraoperative radiotherapy. (36,37) Petersen et al. (2002) reported a 5-year recurrence-free period in 58% of cases after the application of intraoperative radiotherapy followed by postoperative treatment. (38) Other authors give preference only to intraoperative radiotherapy. (36,39,40) Our clinic increasingly relies on the combination with radiotherapy performed in close collaboration with radiologists, who have started a prospective study on this matter. For large tumors with low differentiation we consider preoperative radiotherapy necessary. However, despite the evidence to date there are no large randomized studies demonstrating the role of radiotherapy for retroperitoneal soft tissue sarcomas. The role of chemo-

therapy is still controversial. (41) Researches on the benefits and disadvantages of adjuvant and neoadjuvant chemotherapy continue. So far it is not applied as a standard, but rather in the context of clinical trials. In this study, only three patients were included in programs with Doxorubicin and a result was achieved in only one case. In the other two patients the treatment was stopped due to the development of complications. Chemotherapy is the method of choice in patients with advanced soft tissue sarcomas and the goal is to downstage the tumor to a resectable one or simply to relieve the symptoms. (41) Postoperative chemotherapy is beneficial for patients with microscopically positive resection margins, especially in cases with low-grade sarcomas. It is useful in patients who are unsuitable for radiotherapy (for example cases with severe radiotoxicity). Differences were found as different chemosensitivity of various histological subtypes. Many studies do not provide convincing results of chemotherapy, because of which some authors do not support its use in retroperitoneal soft-tissue sarcomas. (3,5,7) In Bulgaria the use of radio- and chemo-therapy in primary retroperitoneal tumors came into practice over the past recent years, but they are not routinely applied. This is probably due to the lack of an algorithm for the treatment of soft-tissue tumors, and because of the large spread of cases across the country, often operated in regional or municipal hospitals with insufficient experience and knowledge about the specifics of these neoplasms. From these data, it appears that local recurrence and presence of distant metastases and the ability of performing radical extirpation respectively are the main determinants of life expectancy. We, like many authors, emphasize the importance of early diagnosis, which would increase tissue integrity and would improve survival and quality of life.(1,3,8,42) Systematic follow-up and examination of patients are very important. Caution is necessary during the first two years after surgery, but in general the follow-up should extend until the end of the patients' life. The first two years we perform a complete physical examination and CT of the chest, abdomen and pelvis every 3-4 months and then until the end of the fifth year - twice a year. After that tests should be carried out once a year for life.

Conclusion

Local recurrences, the presence of distant metastases and the ability of radical extirpation are the main long-term prognostic factors. Therefore, we think that the optimal strategy for treatment is the performance of radical tumor extirpation with subsequent follow-up every 3 months in order to early diagnose relapses and distant metastases. If they are diagnosed preoperatively radiotherapy may be useful in order to increase the ability for radical resection of the tumor.

Conflict of interest

The authors declare that they have no conflict of interest.

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