Survey among German Gynecologists on the Clinical Management of Patients with Sarcomas of the Uterus

FRANK CHIH-KANG CHEN, MATTHIAS DAVID, ROLF RICHTER, MUSTAFA ZELAL MUALLEM, RADOSLAV CHEKEROV and JALID SEHOULI

Department of Gynecology, Charité University Medicine Berlin, Campus Virchow-Klinikum, Berlin, Germany

Abstract. *Aim: To gain more information about the knowledge of the clinical management of uterine sarcoma. Materials and Methods: This survey was performed among members of the North-Eastern German Society of Gynecological Oncology (NOGGO) and the German Society of Psychosomatic Medicine in Gynecology and Obstetrics (DGPFG) on the treatment of uterine sarcomas. Results: Altogether, 374 gynecologists took part. When asked about the surgical therapy of leiomyosarcoma, 64% indicated hysterectomy with bilateral adenectomy and lymph node dissection. Answers on the extent of lymphadenectomy in leiomyosarcoma differed widely. When asked about the preferred chemotherapy regimen for metastatic uterine sarcoma, more than 60% of all gynecologists would not apply any chemotherapy. Almost 40% recommended any kind of radiotherapy in this situation. Conclusion: There is a great uncertainty about the standard treatment of uterine sarcoma, even among specialists of gynecological oncology. It is time for organized efforts to improve the treatment of uterine sarcoma.*

Uterine sarcomas comprise 1% of all gynaecological malignancies and account for 2-6% of uterine malignancies, with an incidence of 1.7 in 100,000 women (1-3). The chance of survival is still low, with 5-year survival rates of 50-70% for patients with stage I uterine sarcoma and 0-20% for the remaining stages (4). Uterine sarcomas constitute a rare, but highly malignant group of tumors, arising from the smooth muscle or connective tissue of the uterus. The three most common subtypes are carcinosarcoma (CS) (also named malignant mixed Müllerian tumor; 50%), leiomyosarcoma (LMS) (30%) and endometrial stromal sarcoma (ESS, 15%). The recent development of a new Fédération Internationale de Gynécologie et d' Obstétrique (FIGO) staging system (5) and recent efforts to define tumor stages for each tumor entity (6) have allowed each type of uterine sarcoma to be treated separately. CS arise as undifferentiated tumors of the original organs and should be treated like these tumor entities as they comprise both malignant epithelial and malignant sarcomatous components. Most women with CS can undergo surgical treatment according to the preoperative staging of the tumor. Simple hysterectomy has been recommended for women with stage I uterine carcinosarcoma because no survival differences in patients with stage I disease who underwent simple *vs.* radical hysterectomy were found (7). Radical hysterectomy can be considered for women whose tumors have spread to the cervix or parametrial tissue (8). Bilateral salpingo-oophorectomy and systematic lymphadenectomy are often recommended, despite a lack of evidence for an improved overall or progression-free survival following radical surgery. As for systemic therapy in metastatic and stage II-IV carcinosarcoma, combinations of platinum with ifosfamide, doxorubicin with ifosfamide, and ifosfamide with paclitaxel have proven to be effective. In addition, there is indirect evidence for the efficacy of a combination of carboplatin and paclitaxel (9). The standard basis for surgical treatment for uterine leiomyosarcoma (LMS) is simple hysterectomy. In post-menopausal women, bilateral salpingo-oophorectomy is recommended. Lymph node dissection in women with lymph node metastasis or in those with confirmed early-stage LMS did not have a therapeutic benefit according to previous studies (10). Therefore lymph node dissection should be considered only in women found to have macroscopic lymph node metastasis or extrauterine disease during surgery (11), but the impact on overall survival is still unclear. For chemotherapeutic approaches to metastatic LMS, there are only few data from small studies showing some effects of doxorubicin, ifosfamide, gemcitabine, docetaxel or trabectedine (12-16). Recently, pazopanib gained FDA approval for the second-line treatment of patients with soft tissue sarcoma following the results of the PALETTE study (17). The standard basis for surgical treatment for uterine ESS is also simple hysterectomy. Because it is a low-grade

Correspondence to: Jalid Sehouli, Department of Gynecology, Charité University Medicine Berlin, Campus Virchow-Klinikum, Augustenburger Platz 1, 13353 Berlin, Germany. Tel: +49 30450564002, Fax: +49 3045564902, e-mail: jalid.sehouli@charite.de

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malignancy with an indolent course compared with high-grade uterine sarcomas, fertility-preserving surgery has been suggested in some case reports and does not seem to affect the outcome of pre-menopausal women (18). ESS are rare tumors accounting for only 6-20% of all uterine sarcomas (19-21). CS have the strongest indication for adjuvant radiotherapy, especially for early-stage disease. Women with LMS and ESS receiving adjuvant radiotherapy take advantage of improved local control of the tumor compared with women undergoing surgery alone (22, 23).

Hence, it was the objective of this study to evaluate the knowledge on uterine sarcomas, especially of their treatment. Therefore, a survey was performed among German gynecologists who were members of the North-Eastern German Society of Gynecologic Oncology (NOGGO) and the German Society of Psychosomatic Medicine in Gynecology and Obstetrics (DGPFG). This questionnaire comprised of two parts: questions focused on attitudes towards hysterectomy for benign uterine tumors in the first part, and treatment of LMS and uterine CS in the second part. The results of the first part of the study have already been published (24).

Table I. *Socio-demographic data of German participants (n=374).*

Traits of interviewees	Number and (%) or median and (range)
Gender	
Female gynecologists	225 (60%)
Male gynecologists	149 (40%)
Age, years	
All	50 (27-84)
Female	50 (27-84)
Male	51 (30-82)
Years in specialty	
All	16 (0.3-50)
Female	15 (0.3-50)
Male	17.5 (1-42)
Member of	
NOGGO (oncologists)	134 (36 %)
DGPFG (psychosomatic medicine)	240 (64%)
Status of occupation	
Private clinic	219 (63%)
Employed at a hospital	113 (32%)
Not practising currently	17 (5%)

Materials and Methods

In 2010, we performed a survey among members of the NOGGO and the DGPFG, which was part of a greater survey with the title "Attitude of German Gynecologists Towards Hysterectomy" (24).

A questionnaire was sent by letter to all members of the NOGGO (n=613) and the DGPFG (n=785) to their occupational address, either at their hospitals or their private clinics, during the months of March and April of 2010. All recipients were gynecologists. The questionnaire consisted of 36 questions about sociodemographic and professional parameters of the gynecologists including age, gender, speciality, years of experience, type of work (clinic, hospital), as well as the number of hysterectomies performed and their attitudes towards hysterectomy. Additionally, eight questions were asked about the treatment of uterine sarcomas which were analyzed in this study. These questions were applied to 10 physicians during a pilot phase before the actual study started. For statistical analysis we used the statistical program SPSS for Windows 18.0 (by IBM, Amonk, New York, USA). None of the analyzed parameters exhibited a Gaussian distribution, hence medians and interquartile ranges are given instead of means. For statistical analysis of differences between subgroups, the Kruskal Wallis test was used for continuous variables, and the χ^2 test combined with Fisher's exact test was used for discrete variables. Statistical significance was established at probability (p) <0.05. Adjusted odds ratios (OR) with corresponding 95% confidence intervals (95% CI) were obtained using logistic regression analysis.

Results

Altogether, 374 gynecologists took part in the greater survey, resulting in a return rate of 30.6% among DGPFG members and 21.8% of NOGGO members (Table I). Among all, 116 (31%) gynecologists stated not to have treated a single patient with uterine sarcoma at all (Figure 1) within the previous year. Fewer gynecologists from the DGPFG compared to members of the NOGGO admitted not having dealt with patients with sarcoma within the previous year (62.6 *vs.* 29.5% for LMS, $p<0.001$; 78.0 *vs.* 23.6% for CS, $p<0.001$, and 85.4 *vs.* 54.5% for ESS, $p<0.005$). Together with those 75 gynecologists who did not answer the question at all, altogether 191 did not answer this question or had not treated a single patient with uterine sarcoma the year before. The total number of participants who did not answer the question or stated not to have treated a patient with this diagnosis was n=226 (60.5%) for LMS, n=257 (68.7%) for CS, and n=314 (83.9%) for ESS. The percentage was significantly lower among members of the NOGGO than of the DGPFG (in detail: 38% *vs.* 72.9% for LMS, 39.3 *vs.* 86.3% for CS, and 70.1 *vs.* 91.7% for ESS, $p<0.001$). It was also lower among male compared to female gynecologists, gynecologists >45 years than among gynecologists <45 years, and gynecologists with surgical experience compared to gynecologists who declared not to have performed hysterectomies in their professional career. After multivariate logistic regression, membership of the NOGGO and surgical experience were independent influencing factors with OR of 2.0 for NOGGO members ($p<0.05$) and 2.9 for gynecologists with surgical experience ($p<0.005$). More detailed questions concerning treatment modalities were answered by 239 gynecologists for LMS (63.9%), by 227 gynecologists for CS (60.7%) and by 225 gynecologists for ESS (60.2%). When asked about the standard operative therapy of LMS, 64% defined hysterectomy with bilateral adenectomy and lymph node

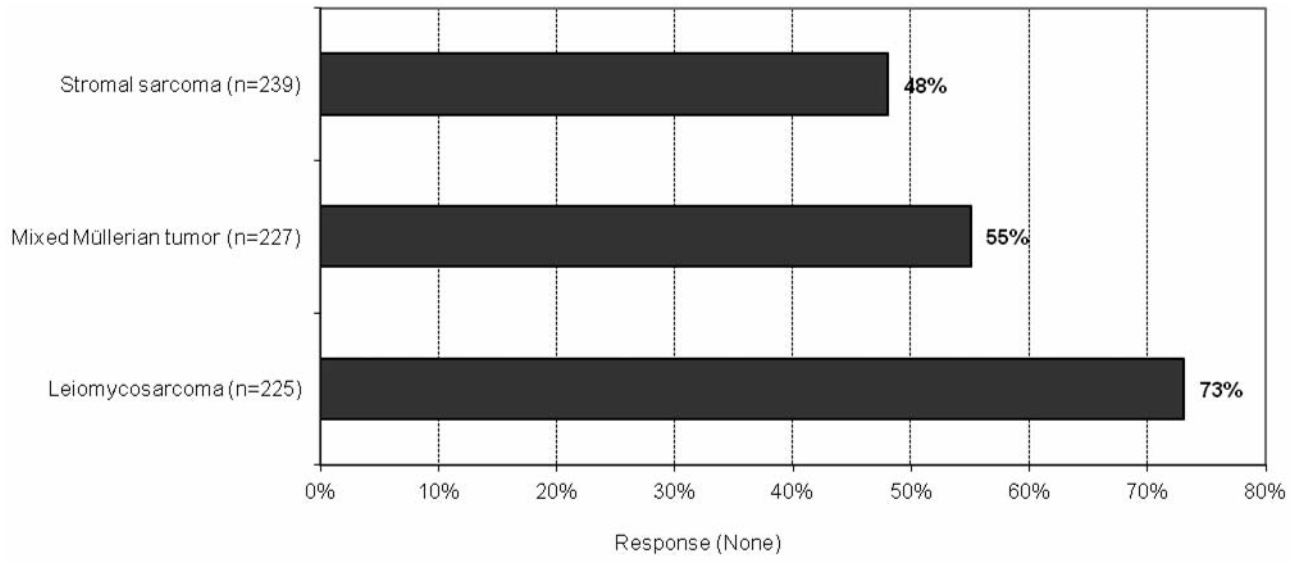

Figure 1. *How many patients with sarcoma have you treated in the past year?*

dissection, 21% chose hysterectomy with bilateral adenectomy and 11% simple hysterectomy (Figure 2). Of note, among members of the DGPFG, lymph node dissection was chosen significantly more frequently than among members of the NOGGO (76.2% *vs*. 49.5%, $p<0.001$). Only membership of a gynecologic-oncological organization proved to be an independent factor for choosing hysterectomy without lymph node dissection, with an OR of 2.4. Given the question "To what extent do you perform lymphadenectomy in leiomyosarcoma?", 29% answered that they performed lymphadenectomy with the strategy of lymph node 'sampling', 19% chose pelvic and 18% pelvic and para-aortic lymphadenectomy (Figure 3). When asked about the primary goal in performing lymphadenectomy in LMS (multiple answers allowed), 71% answered hey undertook lymphadenectomy for diagnostic purposes, 50% considered the result of lymphadenectomy as a decision tool when deciding on adjuvant therapy, 45% intended an improvement of progression-free survival and 27% of overall survival. Faced with the question for the chemotherapy regimen in metastatic LMS, among 239 gynecologists who gave an answer, 10% preferred platinum plus ifosfamide, 8.8% preferred carboplatin, and paclitaxel and 9% other combinations, such as carboplatin and pegylated liposomal doxorubicin, docetaxel and gemcitabine, paclitaxel and ifosfamide, a platinum-based monotherapy, or trabectedine monotherapy. Another 7% marked different alternatives. The majority of all gynecologists, 63%, would not apply any chemotherapy for metastatic LMS. There was a great difference between specialists in gynecological oncology, of whom only 35.9% stated they would not recommend any chemotherapy *vs*. 83.8% of specialists in psychosomatic gynecology who favored chemotherapy ($p<0.001$). This difference was even larger when we asked for the preferred chemotherapy regimen for metastatic CS: 60% voted against any chemotherapy, but even through 87% of DGPFG members *vs*. 22.9% of NOGGO members ($p<0.001$) opted against chemotherapy, 12% would give a combination of carboplatin and paclitaxel, and 8% of carboplatin and ifosfamide (Figure 4). Following logistic regression, NOGGO membership was an independent factor for the recommendation of chemotherapy, with an OR of 5.3 ($p<0.001$) for LMS and of 12.3 ($p<0.001$) for CS. When asked, "Do you advise adjuvant radiotherapy in leiomyosarcoma?" almost 40% stated recommending some form of radiotherapy, either as a combination with chemotherapy (11%), or as external radiotherapy (10%), as a combination of external and brachytherapy (11%), or solely as intra-cavitary radiotherapy (6%). Sixty-one percent of all gynecologists who answered this question would not recommend radiotherapy and there was no significant difference between the members of the two societies. When asked about the objective for radiotherapy (multiple answers allowed), the aims given were risk reduction or recurrent cancer for 76%, improvement of progression-free survival in 56%, and improvement of overall survival in 31%.

Discussion

Uterine sarcomas are so rare that many gynecologists, if not working at oncology centers, never see a patient with this malignancy and do not know much about their

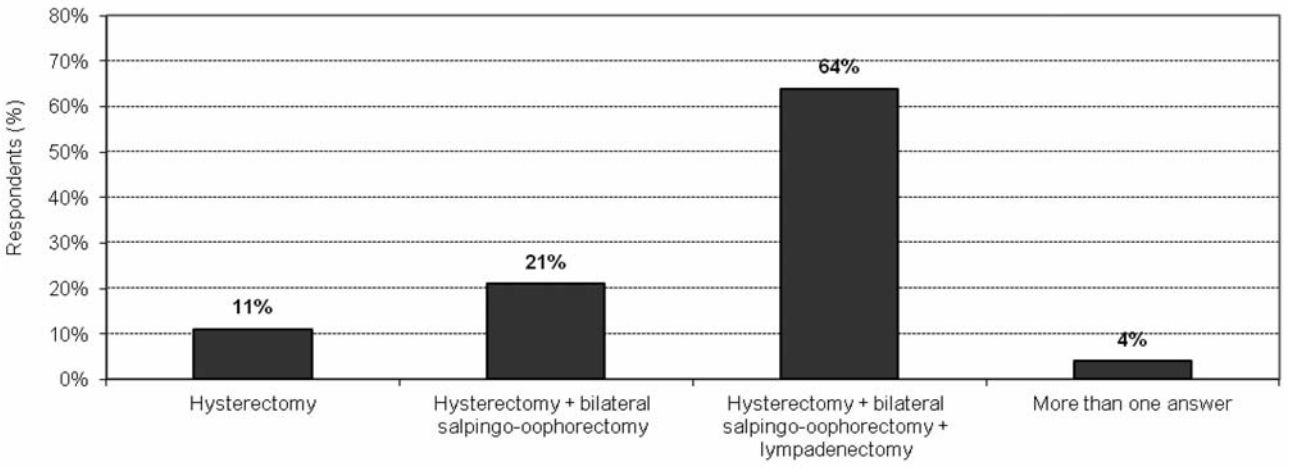

Figure 2. *Which is your routine surgical treatment for leiomyosarcoma? (n=239).*

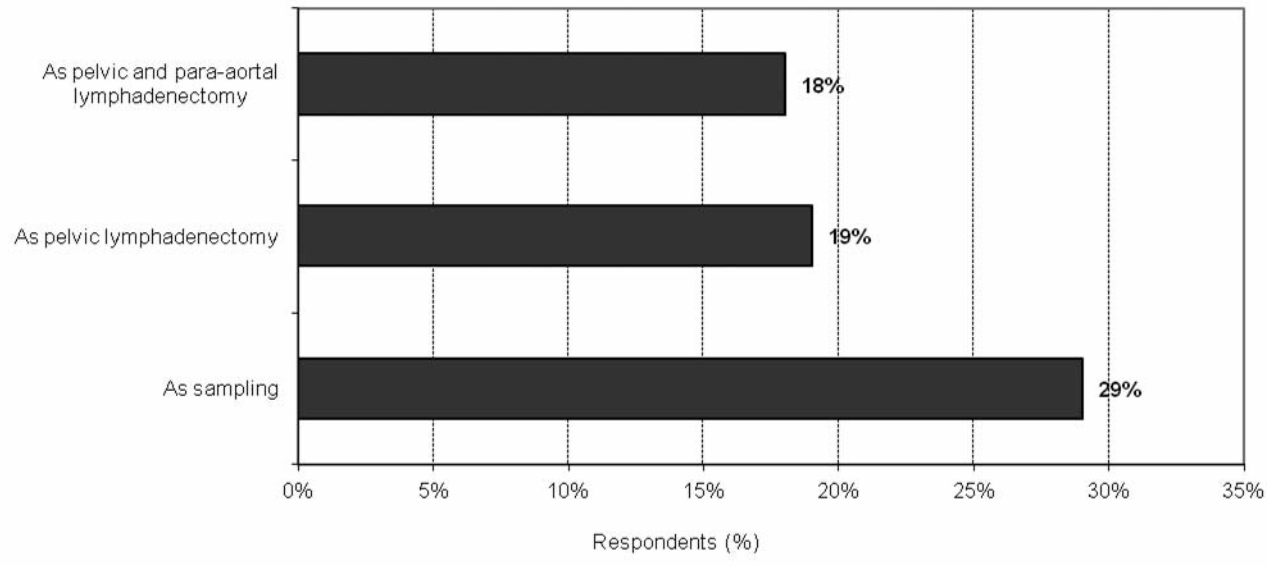

Figure 3. *To what extent do you perform lymphadenectomy? (n=194).*

standard treatment. In Germany, there are not even guidelines from national organisations for the treatment of uterine sarcoma. Therefore, we performed a survey among German gynecologists to investigate their knowledge of treatment of uterine sarcoma. The uncertainty while dealing with uterine sarcomas is reflected by the fact that not more than two-thirds of all participants answered the questions on uterine sarcomas and their subtypes. And among them, more than half admitted to not having treated a single patient with uterine sarcoma within the previous year, although all of them were gynecologists and about one-third were members of a society for gynecological oncology. With these preconditions, it comes as no surprise that when asked about the routine surgical treatment for LMS, only one fifth chose hysterectomy with bilateral salpingo-oophorectomy, a procedure that represents the state-of-the-art and standard therapy recommended by the Austrian Working Group of Gynecological Oncology. Similarly, there was a wide range of answers concerning the objective and extent of lympadenectomy and only a few gave the 'right' answer. At least, more than half of the respondents considered lymphadenectomy only for diagnostic purposes when asked about the primary goal in performing lymphadenectomy. This result is all the less

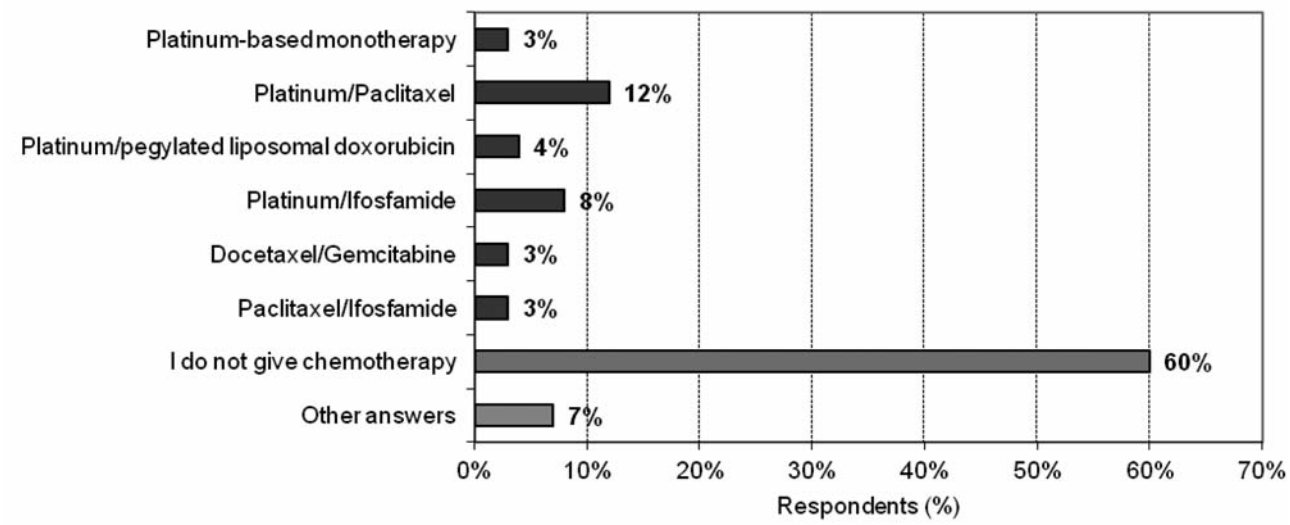

Figure 4. *Which is your favourite chemotherapy regimen in metastatic carcinosarcoma? (n=227).*

astonishing as multiple answers were allowed and after all, almost half of all who answered hoped for improvement of progression-free survival and many more for improvement of overall survival. As yet, there are no data available to support an improvement in patient survival by systematic lymphadenectomy. When asked about chemotherapy and the preferred chemotherapy regimen for metastatic LMS, only one third would give any chemotherapy. The majority of all gynecologists would not apply any chemotherapy in metastatic LMS. Only about 3% voted for the standard regimen of docetaxel and gemcitabine and only about one fifth for a combination therapy including substances that had been proven to be effective such as doxorubicin, ifosfamide, gemcitabine, docetaxel or trabectedine (25, 26). Similarly, in metastatic CS, most participants voted against any chemotherapy, only 15% preferred a regimen that had been proven to be effective in metastatic and stage II-IV carcinosarcoma such as a combination of platinum and ifosfamid or doxorubicin and ifosfamid or ifosfamid and paclitaxel (27-31). Of note, more than 80% of gynecologists with non-oncologic specialization did not support chemotherapy in metastatic LMS or CS. For progression-free and overall survival of patients with metastatic sarcoma, patients should seek therapy at a regional center with oncologic experts. The situation is clearer in the field of radiotherapy in LMS. As shown in an (EORTC) phase III trial, adjuvant radiotherapy does not improve progession-free or overall survival and should not be generally recommended (32). More than 60% would not recommend adjuvant radiotherapy in patients with LMS and act in keeping with the guidelines, and no special oncologic or surgical experience is needed to have this knowledge according to our results. This figure eases the fact that of those who recommended adjuvant radiotherapy, 56% hoped for progression-free survival and almost one third for an improvement of overall survival which lacks any scientific evidence. It is clear there is a great uncertainty about the standard treatment of uterine sarcomas with the consequence that a high percentage of gynecologists do not even answer medical questions on uterine sarcomas although they responded to questions on hysterectomies. There is room for improvement regarding the distribution of knowledge of rare malignant diseases in gynecology. However, this lack of knowledge only reflects the lack of evidence-based clinical trials in this field. With many new substances for the targeted therapy of uterine sarcomas arriving, some of them already with FDA or EMEA approval, such as trabectedine, or with promising clinical data, such as sorafenib, pazopanib, and bendamustine, it is time for organisational efforts to improve the multimodal treatment of uterine sarcomas by establishing national disease centers and implementing regionalization, as well as running educational programs.

Conflicts of Interest

We hereby declare that there are no conflicts of interest for any of the Authors.

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