Abstract. Borderline ovarian tumour (BOT) represents a rare and special tumour entity. Despite a generally favourable prognosis for patients with BOT, the presence of invasive peritoneal implants decreases the survival rate to 30-50%. In contrast to ovarian cancer, only few data exist concerning the current clinical management of patients with BOT. For this reason, the present analyses were performed for patients with BOT who were admitted into our online tumor conference for patients with gynaecological malignancies. Based on the results discussed in this article, the current aspects and problems regarding the diagnostic, surgical and conservative treatment and aftercare management of patients with BOT are considered.

Borderline tumours of the ovary (BOTs) represent a characteristic type of malignant ovarian tumours, but most importantly, they do not show any destructive stromal invasion (1, 2). BOTs constitute about 8-10% of all ovarian tumours, with an incidence of 1.8-4.8 out of 100,000 women per year (3, 4). The mean age at time of diagnosis is approximately 10 years younger than that of women with malignant ovarian cancer, with mostly very favourable prognosis (5, 6). Borderline ovarian tumours are staged according to the FIGO (Fédération Internationale de Gynécologie et d’Obstétrique) classification of ovarian tumors (3, 7, 8). Currently, no reliable diagnostic methods are able to discriminate accurately between a borderline tumour and an early carcinoma of the ovary (2, 4, 9-12). A specific histopathological feature of BOT is the detection of extraovarian invasive, but also non-invasive implants, with different impact on the patient outcome (2). Non-invasive implants are found in a great number of patients with BOT, while only 6% of the women present invasive implants which are strongly associated with a poorer prognosis (1, 13, 14). In the clinical management, the observation of non-invasive implants appears to have no influence on clinical outcome (1, 14-16). The current state-of-the-art treatment of BOT includes the surgical resection of the tumour and extensive peritoneal biopsies of all parts of the abdomen (17, 18). However, the postoperative management protocol is not yet clear (2, 19). Currently no medical therapy has been shown to improve the outcome, thus adjuvant systemic chemotherapy is nowadays not generally indicated for patients with BOT (2, 13, 18-20). In contrast to ovarian cancer (21, 22), there are no prospective trials available and only a few surveys exist concerning the current BOT management. The following analyses of patients with BOT presented to our second opinion centre will be used to discuss physicians’ uncertainty towards the clinical management of BOT with regards to comprehending the demand for further education and training.

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Key Words: Borderline ovarian tumour, clinical management, tumour board.
Patients and Methods

As a basis of discussion concerning different aspects in the current management of BOT, we made use of the clinical data and therapy recommendations of 22 patients presented to the online tumour conference “Gynecological Malignancies” at the Department of Gynaecology, Charité Campus Virchow, University Hospital Berlin, Germany. The online tumour conference was established in 2004 as a pilot project for oncological health care. The meetings are scheduled every two weeks to discuss complex cancer cases which require an interdisciplinary approach. Detailed methodical and specific procedures have been published previously (23). Specialists from the Departments of Gynecology, Surgery, Radiology, Anaesthesiology, Urology, Pathology and Oncology from our University Hospital participate regularly in the tumour boards. Approximately 97 other external gynaecological hospital divisions, as well as 64 general practicing gynaecological oncologists German-wide are also taking part in this global project regularly.

The criteria for case presentation at the tumour board meeting include all gynaecological cancers, pre-invasive diseases which were operated on, and also patients with complex co-morbidity constellations. Special web-based software has been developed for this project in cooperation with the Alcedis Clinical Research Organisation, Giessen, Germany. The software provides all features for an efficient submission and management of clinical data. A main feature is the facility to process and convert different formats of patients’ documents into a format which can be displayed in a conventional web-browser. Data security of the system complies with national standards and recommendations. All patient data are transmitted in an anonymous fashion. Upon formal registration, each participant may freely submit new cases to the tumour board. The screening process and the monitoring of updates of international guidelines and national standards are conducted by an exclusive tumor conference manager. All clinical data and access to the databases is possible online 24 hours a day. For each conference, protocols are generated automatically and made available to the participants (23). This concept of tumour conference was developed by J.S. We prospectively reviewed within six months queries involving the follow-up of the patients and the therapy compliance applied.

SPSS for Windows (version 15.0) was used for statistical evaluation. The present investigation was carried out for the generation of a hypothesis only. For this, all analyses were worked out in a primarily descriptive manner.

Results and Discussion

We have performed a preliminary analysis of treatment recommendations within our interdisciplinary tumour board in order to discuss uncertainties in the clinical routine practice concerning the current management of borderline tumours. Tumour conferences are an important instrument in clinical practice (24-26). Nevertheless, there are very limited data available on the results and implementation of tumour boards in clinical practice (24, 27, 28).

During the period from December 2004 to October 2008, 90 online tumour boards took place and 278 cases were presented. Ovarian cancer was the most common diagnosis (92 cases), followed by 41 patients with cervical cancer and 46 patients with endometrial cancer. In the same period, 22 patients with BOT were presented to the online tumour conference. This represents 7.9% of all patients’ cases discussed, and reflects the importance of BOT in gynecological oncology. The analysed clinical data of these 22 patients (13 primary diagnosis and 9 with recurrence) were used as a basis to discuss the different aspects in the clinical management of BOT with special focus on surgery and systemic chemotherapy.

Surgery. The most preferred questions in the presented BOT-cases were focused on surgical aspects (n=13, 59.1%). Many of the requests have focused on the standards of a staging surgery in the context of the primary treatment (n=10, 45.5%), but also about fertility-sparing techniques (6 cases), lymph node dissection (4 cases) and second look laparoscopy (one case) (Table I).

Despite the fact that the therapy of BOT leans closely on the clinical management of ovarian carcinoma and is directed at definitive surgical staging, i.e. complete or maximum tumour debulking, the treatment of BOTs does show some specific differences (4, 17, 18, 29). According to the FIGO classification, the state-of-the-art surgical treatment includes a detailed surgical exploration of the entire abdomen, bilateral salpingo-oophorectomy, hysterectomy, omentectomy, peritoneal biopsy and lavage (or an ascites sample) or tumour debulking resection of all suspected peritoneal lesions (18, 30, 31). Most of the patients in our series presented a serous-papillary histology, whereby two patients presented mucinous, two mixed and one case with endometrioid histology of BOT. For mucinous tumours, an appendectomy should be performed to exclude any ovarian metastasis of possible mucinous tumour of the appendix (17, 18, 30, 31). In many cases of our analyses, an accurate tumour classification was not possible due to incomplete surgical staging. In 7 out of 14 patients (50%) with a primary diagnosis of BOT, peritoneal biopsies were not taken. In 6 cases (37.5%), invasive implants were documented. Seven patients (50%) presented non-invasive implants (Table I).

The median age of the patients with BOT was 45 years, with a range between 21 and 74 years.

In contrast to patients with ovarian cancer, most of the patients where BOT was diagnosed are generally younger and thus want to be diagnosed at an early tumour stage I (3, 5, 8, 32, 33). The median age of patients with ovarian cancer is generally between 59 and 63 years (7).

Therefore upon desire to preserve fertility, all conservative surgical options must be heeded (31, 34-36). If a BOT has been diagnosed without the presence of invasive implants, after an intensive patient consultation, the following procedure can be chosen in an individual manner: a detailed
exploration of the abdomen, a peritoneal lavage, peritoneal biopsies from all regions of the abdomen, an unilateral salpingo-oophorectomy, an omentectomy, and in addition for mucinous BOT an appendectomy (18, 30). According to current studies evaluating conservative surgery in this group, high conception rates were achieved after a simple ovarian cyst resection (13, 15, 19, 34, 35), but the high risk of local recurrence being up to 75% will still limit the routine implementation (33). For that reason, ovarian cystectomy or a partial adnexectomy has to be performed after careful consultation of the patient about the recurrence risk and provided that the patient is willing to undergo a careful and prolonged follow-up (37). Furthermore, the increasing potency of modern approaches of maintaining fertility should always be discussed (38), although cryoconservation of oocytes of patients with semi-malignant ovarian tumours still remains in general a rarity. A routine recommendation for completion of the hysterectomy cannot be recommended because of lack of a validated benefit for the patients (17, 39).

On the one hand this is due to the fact that following conservative surgical management of BOT, the patient outcome is still excellent; on the other hand rare recurrences usually exhibit a peritoneal location 5, 30, 33).

The systematic pelvic and para-aortic lymph node dissection, which is generally recommended for patients with early stage ovarian cancer and advanced disease without any macroscopic postoperative residuals, is however not recommended in the guidelines for BOT (18, 30). In contrast to an ovarian carcinoma, invasion in the lymph nodes and metastatic spread of BOT are quite seldom and usually non-invasive (4, 17, 40). Moreover, it is not yet clear whether these lymph node implantations represent real metastases, in situ transformed secondary Muellerian-epithelia, or hyperplastic mesothelial cells (1, 5, 9, 14, 16). Concerning the lymph node resection, at least 20% of the patients with FIGO stage I have to be upgraded as belonging to FIGO stage IIc, but there is no evidence for effects of lymph node dissection on the prognosis (2, 15, 39, 41). In two cases of our collective a systematic lymph node dissection was performed prior to consultation with our centre. Retrospectively, this was not indicated (histology shows no lymph node involvement). Again, the most important aspect in the prognosis of patients with BOT is the adequate diagnosis or exclusion of invasive implants.

Systemic therapy. In 15 cases (68.2 %) the question to our conference was about the indication for chemotherapy treatment. In all 9 cases of recurrent BOT the need of further chemotherapy was controversially discussed. But also in two of the presented cases with primary diagnosis of BOT, without any tumour residuals, questions about chemotherapy arose.

In the clinical management of BOT a special approach according to the need of adjuvant cytotoxic treatment is required. Typically and in contrast to patients with ovarian cancer, a relapse in BOT is significantly rare and generally occurs later (15, 20). In this regard, our patients’ median interval between primary diagnosis and relapse was 5 years with a range from 1 to 13 years.

The fact that there are so far no phase III trials which have explored the role of systemic therapy for patients with BOT limits all treatment recommendations. Generally, platin-based chemotherapy regimes were administered among BOT in mono-centre non-controlled phase II trials only (18, 20, 42, 43, 44). For women with stage I and even for patients at a higher stage – but where no invasive implants are present – the recurrence rate and long-term patients’ outcome are generally excellent, and we consider no need of adjuvant therapy in this group (2, 17, 20). Also, for the presence of suspected tumour cells in the peritoneal fluid, adjuvant chemotherapy is not indicated due to its unsafe prediction of real invasive implants and due to its unproven clinical relevance (2, 18).

The situation of advanced stage BOT, where post-operative tumour residuals or invasive implants are however present, needs to be discussed in a different manner. Patients with invasive implants and a short tumour relapse exhibit a significantly poorer survival rate (17). For this “high-risk” patient’s group, various authors recommend platinum-based chemotherapy regimes (2, 43, 45). Thus Gershenson et al. recommend six cycles of platin-based chemotherapy (45) and report a 15% response rate within patients with post-operative tumour residuals. In our opinion, for high-risk patient populations, chemotherapy (carboplatin monotherapy or a combination of paclitaxel and carboplatin) should be discussed critically with the patient. Chemotherapy for these patients is justified when the patient is informed in detail and wishes to have a maximum therapy. Nevertheless, the real effect of chemotherapy on patient outcome for “high-risk” BOT can only be truly assessed in randomized multicentric (international) studies.

Conclusion

There is a high grade of uncertainty in the clinical management of patients with BOT. The various clinical aspects of surgery and systemic therapy, in particular must be discussed in detail in order to prevent any under- or overtreatment in regard to the harming of patients with BOT.

References

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