

Invasive Extra-ovarian Recurrence in Borderline Ovarian Tumour: A Retrospective Analysis

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ABSTRACT

Background: Borderline ovarian tumors (BOT) comprise up to 15-20% of ovarian epithelial neoplasms. Borderline ovarian tumors are histologically characterized as epithelial tumors with a stratified growth pattern but without destructive stromal invasion. Serous and mucinous neoplasms constitute the majority of borderline tumors and occur mostly in women of reproductive age.

Methodology: This is Multi-centric retrograde analytical study. We collected data from 2011-2019 of patients proven as Borderline Tumours of Ovary on Post-operative histopathology & Immunohistochemistry, who had frank invasive recurrence in the form extraovarian adenocarcinoma.

Results: In-total 22 out of 90 patients developed invasive extraovarian recurrence in the form of adenocarcinoma, with none of the patients had Supraclavicular Lymphadenopathy or lung/liver/brain/bone metastasis.

Conclusion: Since currently there is no convincing evidence that adjuvant chemotherapy or radiotherapy confers a survival advantage for patients of Borderline Ovarian Tumours of any stage. Long-term surveillance is recommended.

Keywords: Borderline ovarian tumour, invasive, serous, mucinous, adenocarcinoma

INTRODUCTION

Borderline ovarian tumors (BOT) comprise up to 15-20% of ovarian epithelial neoplasms. [1] Borderline ovarian tumors are histologically characterized as epithelial tumors with a stratified growth pattern but

without destructive stromal invasion. Serous and mucinous neoplasms constitute the majority of borderline tumors and occur mostly in women of reproductive age. [1] Howard C. Taylor, Jr., [2] is credited with the first use of the term “semimalignant tumors” in 1929 for a subset of large ovarian tumors that had an indolent clinical course with relatively favorable patient outcome despite the presence of peritoneal disease. However, borderline ovarian tumors were not considered a distinct entity until 1971 when the International Federation of Obstetric Gynecology (FIGO) established a separate borderline category of tumors. Since then, considerable controversy has surrounded the definition and management of borderline ovarian tumors because of their enigmatic pathogenesis and perplexing biologic behavior. [3] Synonyms of borderline ovarian tumors include tumors of borderline malignancy, tumors of low malignant potential, and atypical proliferative tumors. Several studies have described the characteristic cytogenetics, epidemiology, natural history, and biologic behavior of specific subtypes of borderline ovarian tumors. Researchers have postulated that specific genetic changes contribute to their pathogenesis and stepwise progression to low-grade invasive ovarian carcinomas. Although the majority of serous and mucinous borderline ovarian tumors are characterized by *KRAS* mutations, β -*catenin* and *PTEN* mutations are commonly seen with endometrioid borderline ovarian

tumors. [4] In addition, endometriosis is an important precursor of endometrioid and clear cell borderline ovarian tumors. Prognosis is generally excellent.

Although the imaging features of borderline ovarian tumors significantly overlap with those of invasive epithelial cancers, cross-sectional imaging studies play a major role in the diagnosis, management, and surveillance of patients with borderline ovarian tumors. [5] Serous Borderline tumours are bilateral in one-third of cases. These are associated with peritoneal implants in 35% of cases, of which up to 15-25% can be invasive implants, the omentum being the most common area affected. [6-8, 11] In addition, in advanced stages, these may be associated with lymphatic involvement in about 27% of cases, including the following in descending order of frequency: pelvic, omental and mesenteric, and paraaortic and supradiaphragmatic regions. [6, 7, 12-14] Serous BOT can be further divided into two subtypes: 1) Typical pattern (90%) is often a unilocular cystic mass with fine septa in its interior. 2) Micropapillary pattern (10%) presents specific histological features (micropapillary appearance contiguous over > 5mm or in more than 10% of the tumour). [8, 11] The latter has a worse prognosis since the majority are associated with a higher rate of recurrence in invasive form, a greater percentage of bilaterality and presence of invasive implants, and upstaging when performing restaging surgery. [6, 9, 10, 15] However, the latest publications suggest that serous BOT with micropapillary pattern and without implants (stage I) or with non-invasive implants (II and III) could have the same prognosis as serous BOT without micropapillary pattern. Therefore, malignancy is more closely related to the presence and invasiveness of implants. [7]

Mucinous Borderline tumours tend to be larger than serous BOT and have either a unilocular or multilocular cystic structure, with fine septa in their interior and intramural nodules. [8] Peritoneal implants are very uncommon (15%), and when they

occur, a mixed histology as well as the presence of pseudomyxoma peritonei must be ruled out. These are considered a differentiated entity, in which peritoneal involvement of a mucinous carcinoma is primarily of digestive origin, generally of the appendix. [6, 7] They are divided into two subtypes: 1) Intestinal (85-90%): the majority of these are unilateral and in the case of a bilateral occurrence, primary intestinal cancer must be ruled out. 2) Endocervical or mullerian (10-15%): these are bilateral in at least 40% of cases and 20-30% are associated with ipsilateral endometriomas or pelvic endometriosis, as well as with BOT of mixed histology (seromucinous). [11]

METHODOLOGY

This is Multi-centric retrograde analytical study. We collected data from 2011-2019 of patients proven as Borderline Tumours of Ovary on Post-operative histopathology & Immunohistochemistry, who had frank invasive recurrence in the form extraovarian adenocarcinoma. All patients had undergone pre-operative evaluation with routine blood investigation, contrast enhanced CT-scan of Abdomen with pelvis to know extent of disease & operability, Serum CA-125 as tumour marker (Table 1.1) & X-ray chest to rule out lung metastasis. As all patients had completed family, all patients opted radical surgery in view of explained risk of recurrence & were operated with total abdominal Hysterectomy + Bilateral Salpingo-Oophorectomy + Pelvic Lymph node dissection. Post surgery all patients were under follow-up as mentioned: 3 monthly for first 2 years then 6 monthly for next 3 years & yearly thereafter. At each follow-up, patients were examined clinically & investigated using Ultrasonography (USG) of abdomen with pelvis & Serum CA-125 levels. Cases with abnormal findings on USG or raised level of CA-125 were further investigated with contrast enhanced CT-scan of Abdomen with Pelvis & Thorax.

RESULTS

In-total 90 patients (n=90) were analyzed in present study. Median follow-up period was 5.5 years. The mean age at presentation of Borderline Ovarian Tumour was found to be 35 years. The most common symptom reported by patients was distension of abdomen. On clinical per-abdomen examination hard lump in abdomen was found on palpation. Pre-operative contrast enhanced Computerized Tomography (CECT) scan of abdomen with pelvis confirmed solid cystic lesion originating from either unilateral or bilateral ovary with no Lymphadenopathy/free fluid in abdomen/omental caking/peritoneal caking. Ca-125 level was ranged from 16 to 79 U/mL (details in Table 1.1). In these cases post-operative histopathological & Immunohistochemistry was suggestive of Serous Borderline Ovarian Tumour in 63 cases & Mucinous Borderline Ovarian Tumour. Recurrence was detected within first 2 years of follow-up on CECT scan abdomen with pelvis, raised CA-125 level & confirmed using Image Guided Core needle biopsy. Out of 90 patients, 16 patients developed recurrence as invasive

Serous Adenocarcinomatous peritoneal/omental caking & with malignant ascites. Among these 16 patients 5 patients also had Pelvic or Para-aortic Lymphadenopathy. Out of 90 patients, 6 patients developed recurrence as invasive Mucinous Adenocarcinoma with peritoneal/omental caking, malignant ascites & Pseudomyxoma peritoni. Among these 6 patients none of the patients had Pelvic or Para-aortic Lymphadenopathy. Malignant ascites was confirmed using fluid cytology & cell block cytology. In-total 22 out of 90 patients developed recurrence as mentioned above with none of the patients had Supraclavicular Lymphadenopathy or lung/liver/brain/bone metastasis (Table 1.2).

Table 1.1: Pre-operative range of CA-125 levels against number of patients

Range of CA-125 in U/mL	No. of Patients (n=90)
0-10	00
1-20	12
21-30	10
31-40	32
41-50	26
51-60	05
61-70	04
71-80	01
>80	00

Table 1.2: Characteristics of Invasive recurrence

Characteristics	Serous Adenocarcinoma	Mucinous Adenocarcinoma
No. of Patients	16	06
Omental Caking on CECT	Present	Present
Peritoneal Caking on CECT	Present	Present
Malignant Ascites	Present	Present
Pseudomyxoma peritoni	Absent	Present
Lymphadenopathy	Present	Absent
Supraclavicular lymph node	Absent	Absent
77Organ Metastasis	Absent	Absent
CA-125 level	Range 300-1200 U/mL	Range 200-760 U/mL

DISCUSSION

Regular and intensive follow-up of the patients is essential for the early detection of recurrence in the form invasive disease. This must be conducted for a longer period of time than for patients with ovarian cancer. Studies have reported cases in which extraovarian invasive recurrence and death occurred even after more than 10 years. [16-19] Malignant transformation describes the situation in which borderline tumors develop recurrent disease in the form of

invasive cancer, which is largely dependent on the length of follow-up. Approximately one third of SBTs are associated with peritoneal implants. [16, 17, 20] The prior subdivision of non-invasive and invasive implants has been abandoned in the recent WHO classification, and any invasive foci are now considered peritoneal Low Grade Serous Carcinoma (LGSC) reflecting their similar biologic behavior. [21] The current WHO 2014 classification now designates these foci as LGSC. In addition, implants

lacking an infiltrative growth but displaying other features suggestive of LGSC, should also be designated LGSC. By definition, implants are confined to the peritoneal surface without infiltration of the underlying subperitoneal fat. Of note, omental implants limited to the peritoneal surface can result in merging of lobular clefts, thereby imitating an infiltrative growth pattern. [17, 22, 23] This new nomenclature of extra-ovarian invasive disease is supported by studies demonstrating their similar biologic behavior and disease progression compared to LGSC. [17, 24] Nevertheless, the volume of invasive disease may have prognostic impact. Future studies are needed to clarify the long-term outcome of ovarian SBT associated with small foci of invasive peritoneal disease (LGSC) compared to primary ovarian/peritoneal LGSC presenting with widespread peritoneal carcinomatosis and bulky disease. The size of invasive foci should be stated in the pathology report. Lymph nodes may also contain foci of Serous Borderline Tumour (SBT) similar to their peritoneal counterparts, with individual or clusters of serous epithelial cells with intense eosinophilic cytoplasm located within sinuses, most commonly in subcapsular location. Foci of LGSC with associated desmoplasia and destruction of lymph node architecture have been reported in patients with ovarian SBT and should be classified as LGSC. [21] A recent single-center study including 254 patients with stage-I BOT found a higher incidence of invasive recurrences in Mucinous Borderline Tumour (MBT) compared to SBT however; no unequivocal cases of peritoneal implants associated with MBT have been reported in the literature. Ovarian mucinous tumors are markedly heterogeneous, with frequent co-occurrence of adenomatous, borderline, and carcinomatous components, suggesting a stepwise progression in at least part of the cases. Therefore, careful gross examination and sampling is mandatory and at least one section per centimeter largest tumor diameter should be examined, increasing to

two blocks per centimeter diameter in mucinous tumors >10 cm. [21] Cases with microinvasive foci displaying high-grade nuclear atypia should be designated microinvasive carcinoma according to the recent WHO classification, although the prognostic value of this category remains to be defined. Microinvasion has been reported in 4 to 18% of MBT. [21, 25] Nevertheless, additional sampling as well as immunohistochemical testing are recommended to exclude frankly invasive carcinoma or metastatic disease. MBT with intraepithelial carcinoma has been described in 40 to 55% of MBT and is characterized by areas with high-grade nuclear atypia that differ cytologically from the background epithelium, usually with sharp demarcation & some studies reported a higher recurrence risk. [26-28]

CONCLUSION

Since currently there is no convincing evidence that adjuvant chemotherapy or radiotherapy confers a survival advantage for patients of Borderline Ovarian Tumours of any stage. Hence, long-term surveillance is recommended to document and treat early & late recurrences. Very close monitoring with clinical examination, radiological imaging & tumour marker is required to ensure early diagnosis and treatment for future recurrences.

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How to cite this article: Rewadkar M, Balachandran R. Invasive extra-ovarian recurrence in borderline ovarian tumour: a retrospective analysis. *International Journal of Research and Review.* 2020; 7(3): 397-402.
