ONCOLOGY

Prognostic value of lymph node involvement in ovarian serous borderline tumors

Benedicte Lesieur, MD; Aminata Kane, MD; Pierre Duvillard, MD; Sebastien Gouy, MD; Patricia Pautier, MD; Catherine Lhommé, MD; Philippe Morice, MD, PhD; Catherine Uzan, MD, PhD

OBJECTIVE: This study was conducted to evaluate the prognosis value of lymph node involvement (LN positive) lymph node involvement for borderline ovarian tumor (BOT).

STUDY DESIGN: This was a retrospective study on 49 patients treated at our institution for advanced-stage serous BOT (International Federation of Gynecology and Obstetrics [FIGO] III or IV). Pathological characteristics and survival were compared according to the lymph node status. The same analysis was performed on 1503 patients of the Surveillance, Epidemiology, and End Results (SEER) database.

RESULTS: In our institution, 14 patients were LN positive. Eight patients have been upstaged after lymph node dissection. No patient has died during follow-up (median 53 months). LN positivity was not associated with recurrence. In the SEER registry, 93 patients (6.2%) had LN positivity. These patients were younger and with more advanced local extension. Survival curves were similar after adjustment for FIGO stage.

CONCLUSION: Lymph node involvement does not appear as a prognosis factor for advanced-stage BOT.

Key words: advanced stage, borderline ovarian tumor, endosalpingiosis, lymphadenectomy, prognosis

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Borderline tumors of the ovary (BOTs) or ovarian tumors of low malignant potential represent 15-20% of epithelial ovarian tumors. Described for the first time by Taylor in 1929, they are characterized by a slow clinical course with a potential for peritoneal extension but have an excellent prognosis (overall survival estimated 90% at 10 years), which differentiates them from ovarian cancer. BOTs are also distinct from invasive cancer of the ovary because of the age at onset, which is about 10 years younger.

Extraovarian spread is found in about 35% of cases in the form of peritoneal implants. According to their microscopic characteristics, these implants can be divided into noninvasive (papillary structure similar to that of the BOT) or invasive (a similar structure to that of a well-differentiated invasive adenocarcinoma). Invasive peritoneal implants are associated with a poor prognosis.[1-3]

Although the most frequent extraovarian site of BOT is the peritoneum, pelvic and retroperitoneal lymph node involvement has been described.[1,2,4-9] Since 1995, surgical lymph node staging is no longer among the recommendations for the management of BOTs.[10] Nevertheless, a number of patients undergo lymph node sampling at the time of surgery and lymph node involvement is described in 15-35% of BOTs.[1,2,4,7,8]

We retrospectively collected data on a large series of patients with advanced-stage serous BOTs, all treated in or referred to our institute. The objective of this study was to focus on the prognostic impact of nodal involvement in patients treated for advanced-stage serous BOTs.

We completed this study by consulting the US Surveillance, Epidemiology, and End Results (SEER) database to evaluate the prognosis of patients with BOTs and documented lymph node involvement.

Materials and Methods

From January 1973 to February 2006, 171 patients treated in or referred to our institution for a serous BOT with peritoneal implants had their histological slides reviewed by the same pathologist in our center. BOT was defined as an ovarian tumor with the following: (1) a stratified epithelial lining; (2) the formation of microscopic papillary projections; (3) nuclear atypia; and (4) above all, the absence of frank stromal invasion.[11] The micropapillary pattern was evaluated according to criteria of Kurman et al.[12] A serous BOT with a micropapillary pattern was confirmed if this appearance continuously occupied greater than 5 mm and greater than 10% of the ovarian tumor. Stromal microinvasion can be observed on the ovarian tumor and was defined as the presence of stromal invasion less than 10 mm^2.

The staging classification used was the 2000 classification International Federation of Gynecology and Obstetrics (FIGO).[13] The tumor stage was recorded

From the Departments of Gynecologic Surgery (Drs Lesieur, Kane, Gouy, Morice, and Uzan), Pathology (Dr Duvillard), and Oncology (Dr Pautier and Lhommé), Institut Gustave Roussy, Villejuif, France.

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Reprints: Catherine Uzan, MD, PhD, Institut Gustave Roussy, 39 Rue Camille Desmoulins, 94805 Villejuif, France. catherine.uzan@igr.fr

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using the macroscopic description during the surgical procedure and reviewing the pathology records. Peritoneal implants were classified as noninvasive (epithelial or desmoplastic type) or invasive according to the criteria previously described by Bell and Scully.[14]

Surgery had consisted of either radical (bilateral salpingo-oophorectomy with or without hysterectomy) or conservative treatment (defined as conservation of the uterus and salvaging at least a portion of 1 ovary). Additional staging surgical procedures had occasionally been performed. This was dependent on the surgical teams, on whether the BOT was diagnosed during or after the surgical procedure, and on disease extension. Patients had undergone either an open or laparoscopic approach performed either during a 1-step surgical procedure, if the diagnosis of BOT was made at a frozen section analysis during the operation, or during restaging surgery. Lymphadenectomy, although not recommended, could have been performed because of enlarged nodes or misdiagnosis of invasive carcinoma.

Adjuvant treatment (chemotherapy, external radiation therapy, and chemotherapy with external radiation therapy) had been administered until 1985. The indications for and the type of adjuvant treatment depended on the pathological results (characteristics of peritoneal implants: noninvasive vs invasive), persistent residual tumor, and the date that treatment had been administered.

Seer program database

Case ascertainment. The SEER Program (http://seer.cancer.gov/) currently collects and publishes cancer incidence and survival data from 15 population-based cancer registries that cover one quarter of the US population. Data on more than 6 million in situ and invasive cancer cases are included in the database. The SEER Program is the only source of population-based historical as well as current information on patient survival and disease stage. The mortality data reported by SEER are provided by the National Center for Health Statistics.

From a total of 95,000 ovarian tumors registered, we selected 6017 for further analysis based on the following International Classification of Diseases for Oncology (third edition) codes: 8442 (serous cystadenoma of borderline malignancy), 8451 (papillary cystadenoma of borderline malignancy), 8462 (serous papillary cystic tumor of borderline malignancy), 8472 (mucinous cystic tumor of borderline malignancy), and 8473 (papillay mucinous cystadenoma of borderline malignancy). Only histopathologically diagnosed tumors that represented either the only primary tumor or the first primary tumor diagnosed for each patient were included. Analysis of vital status data were collected until death or the last contact before or until December 2004.

For descriptive purposes, we tabulated data using SEER*Stat software (National Cancer Institute, Bethesda, MD): the variables studied were age, stage (American Joint Committee on Cancer stage third edition), number of lymph nodes examined, number of positive lymph nodes, cause of death, and survival time at recode. Staging of BOT was based exclusively on histologically diagnosed extraovarian lesions (called implants). Implants removed from undesignated sites were coded as abdominal involvement. The presence of implants increased the stage of a BOT, but the data on the subclassification of noninvasive or invasive implants were unavailable.

Statistical analysis

Recurrence-free interval rates were determined using the Kaplan-Meier method. Recurrence-free intervals were calculated including patients who had relapsed. Patients who had died of intercurrent disease were censored at the time of their death. Univariate analysis was performed. The log-rank test was used to compare the survival curves and to determine the P value. A $P < .05$ was considered significant. Categorical variables were compared using the χ^2 or Fisher's test, when appropriate. Continuous variables were compared using the Student t test, the Mann-Whitney U test, or the analysis of variance test, when appropriate.

RESULTS

Our series concerned 49 patients who had undergone a lymphadenectomy and had a final diagnosis of BOT: 14 of them (28.6%) had lymph node metastases from BOT. Patient characteristics and histopathological results are detailed in Table 1.

Forty-five patients had undergone removal of pelvic lymph nodes (PN), 29 removals of paraaortic nodes (PAN): 20 patients had undergone resection of PN alone, 25 had PN plus PAN surgery, and 4 patients had PAN surgery alone. The proportion of patients who had undergone PAN surgery in the group of patients with involved lymph nodes (LN positive) was statistically significantly higher (12 of 14, 85.7%) than in the group with no lymph node involvement (LN negative) with only 18 of 31 patients with PAN (48.6%) ($P = .024$). The mean number of nodes removed was 24.1 in the LN-positive group and 11.3 in the LN-negative group, and this parameter was significantly different ($P = .006$). The 5 patients who had undergone fertility-sparing surgery did not have lymph node involvement.

Regarding operative findings at the time of surgery, macroscopic implants on the omentum were significantly associated with lymph node involvement (28.6% in the LN-positive group, 2.9% in the LN-negative group, $P = .021$). The presence of macroscopic implants on the ovary surface was not associated with LN positivity.

The recurrence rate over the follow-up period was 25% in the LN-positive group (3 of 12) and 23.5% in the LN-negative group (8 of 34). Two of the 3 patients in the LN-positive group had developed an invasive recurrence vs 2 of 8 in the LN-negative group. Only 1 patient had died during the follow-up period, and this death was in the LN-negative group (invasive recurrence 56 months after fertility-sparing surgery when she was 16 years old). Recurrence-free survival and overall survival curves are shown in Figures 1 and 2: 10 year disease-free survival was 67.5% for the LN-negative group vs 79.5% in the LN-positive group; 10 year overall survival was 92.8% for LN-nega-