LAPAROSCOPIC OVARIAN CYSTECTOMY: SELECTION OF PATIENTS AND CONSEQUENCES OF RUPTURE OF OVARIAN MALIGNANCY

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Operative laparoscopy is gaining popularity and widespread application in gynecology. In response to a survey on operative laparoscopy by the American Association of Gynecologic Laparoscopists, the laparoscopic management of ovarian cysts was the third most common procedure reported.[1] Technological advances and appropriate training have allowed ovarian cystectomy to be performed laparoscopically. In this review, we assess the best available diagnostic means to select cases suitable for laparoscopic ovarian cystectomy to prevent inadvertent rupture of ovarian malignancy and to appraise the consequences of rupture of ovarian malignancy if it occurs.

Diagnostic Tests and Selection of Patients

History and Physical Examination

Historically, ovarian cancer has been described as occult disease with an insidious onset of nonspecific symptomatology. A disease of older age, the risk of ovarian malignancy is 12.1 times greater for the 60-69-year age range as compared with the 20-29-age range.[2] And the overall risk of malignancy in an ovarian neoplasm increases from 13% in premenopausal women to 45% in postmenopausal women. The use of a physical examination to differentiate benign from malignant disease is based upon certain characteristics, including bilaterality, presence of cystic/solid components, mobility of the pelvic structures, irregularity of the cyst surface, ascites and cul-de-sac nodularity.[3] However, these characteristics are nonspecific and some (cystic/solid components or irregularities of the cyst) are best addressed ultrasonographically.

Tumor Markers

Circulating tumor markers are used increasingly in the diagnosis and management of gynecologic malignancy. A detailed discussion of tumor markers is beyond the focus of this review. The most commonly used marker for epithelial ovarian cancer is CA 125, a tumor-associated antigen that can be recognized by the specific monoclonal antibody and that is present in 80% of all patients with ovarian cancer. Forty percent of women with Stage I ovarian cancer will have elevated levels.[4] However, it can also be elevated in other physiological circumstances (menstruation and early pregnancy), in benign gynecologic conditions (endometriosis) and with other malignancies (pancreas, stomach, colon and rectum).

To use CA 125 for identifying malignant pelvic masses, O'Connell et al. constructed a receiver operator characteristic (ROC) curve and determined that a cutoff of 35 U/mL achieves a sensitivity of 100%, a negative predictive value of 100%, a specificity of 43% and a positive predictive value of 60%.[5] The ROC curve describes the accuracy of a test over a range of cutoff points by depicting the tradeoff between sensitivity and specificity. It can also compare the validity of different diagnostic tests. In this series, however, it is necessary to consider the possibility of selection bias because of the high clinical suspicion of malignancy that is reflected by the high prevalence of cancer in these patients.

In similar clinical circumstances, Di-Xia et al. found that a cutoff of 194 U/mL (rather than 35 U/mL or 65 U/mL) reduces the false-positive rate from 39.9% and 20.3% respectively to 5.2%.[6] They concluded that a level greater than 194 U/mL represented the 95th percentile for 153 patients with benign pelvic mass and thus could be used to differentiate benign from malignant masses.

These results suggest that a CA 125 cutoff of 35 U/mL is useful for differentiating benign from malignant ovarian neoplasms. However, this usefulness is limited when it is used alone and not in conjunction with other tests.

Ultrasonography

Moyle et al., in research on ultrasonography as a diagnostic test, found a 5% chance of malignancy (one malignancy in 17 patients) in near-total anechoic lesions in their retrospective study of the preoperative ultrasound appearances of 106 ovarian neoplasms.[7] This was

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consistent with their review of the literature (three malignancies in 55 completely anechoic lesions). They also found that sonographic features, such as mixed-density lesions, could be found in both benign and malignant neoplasms.

In a prospective study, Herrmann reported positive predictive values of 73.0% for suspected malignancy (thick septa, irregularity, solid parts, indefinite margins, ascites and matted bowel) and 95.6% for benign lesions,[8] a significant difference in accuracy (P<0.0001). There were no cases of malignancy among 48 purely cystic tumors under 10 cm in diameter.

Sassone et al. created a scoring system based upon the morphological appearance of the lesions (inner wall structure, wall thickness, septa and echogenicity) as depicted by preoperative transvaginal ultrasound.[9] The scoring system achieved sensitivity, specificity and positive predictive value of 100%, 83% and 37%, respectively, in discriminating benign from malignant pelvic masses.

In conclusion, ultrasonographic imaging can exclude malignancy in unilocular and completely cystic masses in the majority of cases and can be suggestive of malignancy when other morphologic features of the cyst are present.

Transvaginal Color Flow Imaging

Bourne et al. published their novel finding that th ey could differentiate between primary ovarian cancer and many benign pelvic masses with transvaginal color flow ultrasonography.[10] Evidence of neovascularization was sought in the masses and the vascular pulsatility index was calculated. Lack of neovascularization and a high pulsatility index were able to exclude the presence of invasive primary ovarian cancer. Folkman et al. had previously shown that angiogenic activity precedes the development of tumor in hyperplastic pancreatic islets in transgenic mice.[11] Two other clinical studies substantiated Bourne's findings.[12,13]

Kurjak et al. calculated prospectively the resistance index (another quantitative waveform assessment) for 743 (74%) of 1000 postmenopausal women.[14] The sensitivity and specificity of the resistance index in distinguishing benign masses from malignant were 96% and 95% respectively; the positive predictive value and the negative predictive value were also 96% and 95% respectively.

From these studies, it is clear that transvaginal Doppler waveforms demonstrate high diastolic flow or low resistance patterns in cases of ovarian malignancy. This is due to the decreased muscle contractility of the newly formed blood vessels, which leads to an increased blood flow in diastole and increased arteriovenous shunting.

New advances are providing evidence that transvaginal Doppler ultrasound is a new and potentially powerful adjuvant technique to differentiate benign from malignant ovarian cysts, particularly those cysts that possess ultrasonographic features suggestive of malignancy and especially cysts in postmenopausal patients. Further studies are needed to confirm its clinical usefulness. One limiting factor in premenopausal patients is the high false-positive rate of the test. It may prove to be helpful to perform the test in the proliferative phase of the cycle, so as to decrease the likelihood of a coexisting corpus luteum.

Combination of Tests

Diagnostic accuracy can be improved by testing serially, to increase specificity and decrease sensitivity, or in parallel, to increase the sensitivity and decrease the specificity, provided that the tests are independent.[15] Finkler et al. assessed the value of combining the results of clinical examination, CA 125 assay, original ultrasound and reviewer ultrasound.[16] The reviewer ultrasound was scored by a 10-point system and the test results were assessed alone and in various combinations. The combination of the CA 125 result with any other positive test in postmenopausal women approached a 100% positive predictive value and significantly improved the negative predictive value.

Another study by Jacobs and coworkers assessed age, clinical impression, and ultrasound scanning by a 5-point score (multiloculation, solid areas, evidence of metastasis, ascites and bilaterality), menopausal status and serum CA 125 as predictors of malignancy.[17] The receiver operator characteristic of each test and of the risk malignancy index (RMI)—the product of CA 125, ultrasound score and the menopausal status—were constructed. The RMI achieved a greater level of differentiation between benign and malignant disease compared to each individual test.

In summary, optimal predictive values that allow preoperative differentiation of benign from malignant ovarian neoplasia can be attained by combining the history and physical examination with the investigations of CA 125 assay, ultrasonography (to assess locularity, echogenicity, evidence of metastasis, ascites and bilaterality) and color flow imaging study. Moreover, adding a laparoscopic assessment will further improve the diagnostic usefulness of these tests. To prevent unwarranted consequences, the beneficial guidance of these tests should be obtained before the gynecologist can decide to proceed to laparotomy or laparoscopic cyst removal. Should such criteria not be heeded, then inappropriate laparoscopic management will occur, as depicted in the following case series.

Gleeson et al. documented three cases of abdominal wall metastases at the trochar insertion site after laparoscopic removal of malignant and borderline malignant ovarian neoplasms.[18] In one patient, there were bilateral ovarian surface excrescences and in the other two patients, aged 69 and 79 years, ascites was detected clinically and ultrasonographically.

How to Avoid Operating on an Ovarian Malignancy by the Laparoscopic Approach

Careful laparoscopic examination of the pelvis and abdomen that reveals ascites, rupture of tumor capsule, tumor on the surface of the ovary, dense adhesions or any other evidence of malignancy is more than enough reason to suspect that the cyst is malignant and thus, not to proceed with puncturing the cyst, even if it appeared anechoic preoperatively. In addition, the following steps will further minimize the risk of operating on a malignant neoplasm by the laparoscopic approach:[3,19-21] 1) Suction the cyst contents, taking care to minimize spillage; 2) macroscopic examination of the cyst contents before sending the specimen for cytology; 3) copious lavage of the peritoneal cavity with sterile water (to lyse malignant cells), followed by adequate suction retrieval to prevent potential dissemination of cancer cells; 4) examination of the interior of the cyst—any solid components or papillae are biopsied and submitted for frozen section; 5) intraoperative detection of malignancy should call for a prompt conversion to laparotomy; and subsequently, 6) the final pathology report is confirmed and checked by the surgeon to ensure that no further intervention is necessary. Failure to prevent rupture of the capsule in cases of malignancy creates a controversial situation.

The Significance of Capsular Rupture and the Effect of Adjuvant Therapy on Subsequent Outcome

We review here the literature pertaining to rupture of the ovarian capsule in cases of malignancy and later prognosis. The circumstances of "rupture" of the capsule of the ovary bear some consideration. Did the rupture precede the surgical intervention? Or, did the rupture occur intraoperatively with minimum manipulation? This may reflect tissue fragility. Was the rupture associated with periovarian adhesions? It may be the result of sharp dissection. At the time of ascertainment of rupture, was there an effort to control the dispersal of fluid? Was the peritoneal cavity lavaged extensively? Was hypotonic solution (cell membrane disrupting) used for irrigation?

At the outset, one can state that few of these circumstances are known. The status of the ovarian capsule with respect to prognosis was assessed in an early study published in 1970 from Duke University Medical Center.[22] Of 262 cases of ovarian cancer, 24% were Stage 1. The pathology was epithelial in 90% of cases. Statistical analysis showed that the state of the tumor capsule was not a determining factor for survival. Furthermore, the use of "prophylactic" radiation or chemotherapy did not alter survival. Although this study was retrospective, and did not deal only with pure epithelial tumors, the numbers were large and statistical methodology was applied.

In 1973, the Mayo Clinic published a retrospective study on the factors that determined the survival of 271 patients with Stage 1 epithelial cancer of the ovary.[23] They concluded that complete surgical removal, unilaterality and low-grade histology were good prognostic factors, whereas high-grade histology, rupture of the cyst, adherence to other structures and extracystic excrescences were poor prognostic factors. This study was performed, in part, before standardization by the FIGO classification came into place. It is difficult to assess whether "rupture" of a cyst was in isolation, or in concert with excrescences and, in particular, whether there was adherence to other structures. Yet it is from this study that "rupture" of the Stage 1 cancer came to be an "accepted" poor prognostic factor.

In 1979, Smith and Day from the M.D. Anderson Hospital reviewed the records of 2115 patients treated from 1944 to 1973 for ovarian cancer (90% epithelial).[24] The analysis of outcomes for the epithelial forms of ovarian cancer showed that stage, grade and presence or absence of ascites were the key prognostic elements for survival. Of interest were 281 Stage 1 patients in whom it was known whether there had been "rupture of the cystic ovarian mass at the time of initial surgery." Of these, 100 had ruptured and 181 had no evidence of rupture. The five-year survival was virtually the same; 69% with rupture and 68% without. By contrast, the presence of ascites at the initial surgery was considered ominous.

In a later analysis of prognostic factors from Sweden published in 1983, the question of rupture was also examined.[25] Over the time period from 1974 to 1978, 494 cases of malignant epithelial tumors were staged according to the FIGO classification. All borderline tumors were excluded. Rupture of the capsule in Stage 1 did not influence the survival, whereas extracystic excrescences led to a significantly lower survival.

In a 1990 paper based on both the Canadian and Norwegian populations, differentiation (grade) was determined to be the most powerful predictor of relapse, followed by dense tumor adherence and large volume ascites.[2-6] After adjusting for these factors, bilaterality, cyst rupture, capsular penetration, tumor size, histologic subtype, patient age, year of diagnosis and postoperative therapy were not of consequence. The disease-free rate was 98% at five years in women with grade 1 tumors in whom both dense adhesions and large-volume ascites were absent. This review concluded in strong terms that in the absence of the ascites, poor histologic differentiation and dense adherence, surgery alone, without adjuvant therapy of any kind, is warranted.

A multicenter trial of outcome of Stage 1 epithelial carcinoma of the ovary (39 patients were Stage 1a, six

patients were 1b and 23 patients were 1c), which gave no adjuvant therapy after comprehensive surgical staging, found that only three patients have had recurrent ovarian cancer.[27] Tumor adherence (of variable degree) and tumor rupture did not alter the prognosis. It was concluded that any clinical trial that is to assess adjunctive postoperative therapy for early ovarian cancer should have a no-treatment arm.

To date, there is no prospective trial showing that rupture of the ovarian capsule in Stage 1 epithelial ovarian cancer will worsen a woman's prognosis. By contrast, the grade of the tumor has been shown consistently to be the strongest determinant of outcome.

Conclusion

The critical concern with the laparoscopic ovarian cystectomy is the possibility of missing cancer. This risk is difficult to determine from the published reports. Nevertheless, it is estimated to be 0.4%.[19,21] We have assessed the best available diagnostic means to enable the gynecologist to select which persistent cysts should be approached by laparoscopy. There has been a substantial effort to differentiate benign from malignant neoplasms using refined diagnostic tests that include high-resolution ultrasonography and tumor markers, as well as new modalities such as transvaginal Doppler technique. Unfortunately, as individual tests, the results have not been encouraging. However, there is more information available from these new modifications of ultrasound findings (scoring systems),[9] transvaginal color flow imaging[10] and the risk malignancy index.[17]

The explicit criteria used to construct the scoring systems (inner wall structure, wall thickness, septa and echogenicity as developed by Sassone and multiloculation, solid areas, evidence of metastasis, ascites and bilaterality as part of the risk of malignancy index developed by Jacobs, as described before), facilitate their application to routine clinical practice. Furthermore, the distinction between benign and malignant cysts can be maximized by combining the history and physical examination, CA 125 assay with a cutoff of 35 U/mL, transvaginal ultrasonography, color Doppler and findings at laparoscopy. Considering these results before making the final decision as to whether to proceed with the laparoscopic cyst removal decreases the risk of operating laparoscopically upon malignant neoplasms. Moreover, following a protocol, as described before, will further minimize this risk.

This selective rather than universal approach is warranted because of the inherent, yet unresolved, consequences of accidental rupture of malignant ovarian tumors. While it is generally perceived that rupture of an ovarian tumor is detrimental, objective evidence for this is inconclusive. To address the effect of rupture on survival and whether it can be ascribed a prognostic value such as for ascites and tumor excrescence as it does in the current staging system, further randomized controlled studies that are stratified for grade and which include a no-treatment arm are required.

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