

WHAT IS THE PROPER WORK-UP OF THE PATIENT WITH CLINICAL EARLY STAGE UTERINE ADENOCARCINOMA?

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Objective

To discuss the proper preoperative workup of patients with uterine adenocarcinoma who present with disease clinically confined to the uterine corpus.

Methods

Review of recommendations suggested in major textbooks in gynecologic oncology over the past thirty five years as well as select recent publications in the gynecologic oncology literature in Asia as well as the United States and Europe.

Results

The suggested preoperative testing for the patient population under consideration has evolved over the years depending on whether the patient is at low risk or high risk for occult metastatic disease.

Conclusion

Standard preoperative testing is always indicated but preoperative CA-125 and advanced radiological imaging are never routinely indicated for "low risk" patients. Either test may be indicated in select high-risk patients in the setting of clinical investigation though it is unclear which test, if either, provides enough meaningful clinical information which will either alter surgical management or which may be justified in light of the predicted high percentage of patients who will have normal preoperative test results.

Keywords: Uterine adenocarcinoma; Preoperative evaluation; CA-125

Cancer of the uterine corpus is the most common invasive pelvic gynecological malignancy in the United States and other industrialized nations, and as a "female" malignancy is exceeded in incidence only by breast cancer. Compared to other pelvic cancers, a greater percentage of patients initially present with disease apparently confined to the uterine corpus (clinical Stage I under the older International Federation of Obstetrics and Gynecology [FIGO] system), in large part because the vast majority of patients with uterine adenocarcinoma first present with abnormal or postmenopausal bleeding and are promptly evaluated and treated. Surgery remains the cornerstone of the initial management for almost all uterine cancer patients.

Despite the relatively high incidence of uterine cancer in industrialized nations and the near-universal agreement that the initial therapy of such patients will be hysterectomy with some degree of surgical staging (reflecting the fact that the current FIGO staging

of uterine adenocarcinoma is now a surgical, not clinical, staging), there is no definitive literature or consensus about what the "proper" preoperative workup should be for the most common

Received: 2012.3.14. Accepted: 2012.3.22.

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type of patient presentation with uterine adenocarcinoma – the patient whose disease appears to be clinically confined to the uterine corpus. It is a virtual certainty that significant differences in the preoperative workup of clinical stage I uterine adenocarcinoma patients exists in different regions of the United States as well as from country to country in the international gynecologic cancer community. Although some of these differences are the result of differences in access to select radiological imaging technologies such as computerized axial tomography (CT), magnetic resonance imaging (MRI), or positron-emission tomography (PET) machines, there are also significant differences in workup within medical communities where these technologies are widely available.

Materials and Methods

The purpose of this paper is to review and evaluate the different recommendations for preoperative workup for the patient with clinical early stage uterine adenocarcinoma in some of the definitive international textbooks in gynecologic oncology as well as select recently published articles in the gynecologic oncology literature to determine which of the many available preoperative testing options should be universally obtained on all patients and which should be used selectively, if at all.

1. A study in contrasts: Korean and United States approaches to the preoperative workup

Since uterine adenocarcinoma is the most common gynecologic malignancy in most Western countries as well as in Korea, one would think that there would be a consensus in the gynecologic oncology literature or community on what the proper preoperative evaluation of the most common patient – the woman presenting with apparent early-stage disease – should be. Surprisingly, this is not the case.

In Korea, many if not most patients with early stage uterine cancer will have a pelvic sonogram, an abdominal pelvic CT scan, and a pelvic MRI; all of these are done in large part because all citizens have national health insurance and the Korean government has agreed to pay for all of this testing [1].

PET-CT scanning is not routinely paid for by Korean national health insurance for uterine cancer but may be offered to patients anyway, with the understanding that it will be paid for out of pocket and might possibly provide additional useful information preoperatively [1].

In the United States the preoperative evaluation of early stage en-

dometrial adenocarcinoma patients is much less uniform. Patients may have all, or none, of the preoperative radiological testing routinely done in Korea. This may depend on patient and physician preference, age of the physician or patient, source of physician training or affiliation, patient income, type of patient insurance coverage, type of hospital in which they receive their care or, and even the region of the United States in which they live.

Results

1. Evolving gynecologic oncology textbook recommendations over time

The variation, and lack of consensus, on proper preoperative testing for patients presenting with clinical early uterine adenocarcinoma might not be so surprising if one looks at the writing on the topic over time in some of the authoritative textbooks on gynecologic cancer. DiSaia et al. [2] first edition (Synopsis of Gynecologic Oncology) published in 1975 does not mention anything about the preoperative workup for patients with early stage uterine adenocarcinoma in the twenty-five page chapter on corpus cancer. When this book was written in 1974, CT scanners were just being deployed in hospitals in the United States, office-based sonography did not exist, and MRI machines had not yet been invented.

By the time the second edition of DiSaia and Creasman [3]'s book was published in 1984 the authors had changed, and some definitive recommendations regarding proper preoperative workup of uterine adenocarcinoma first appear: "Endocervical curettage should be performed in any patient who has not had a fractional curettage. Routine hematologic studies and clotting profiles are obtained on all patients. Presurgical metastatic evaluation should include a chest film, intravenous urogram, and metabolic profiles. Sigmoidoscopy and barium enema have been reserved for patients who demonstrate palpable disease outside the uterus. Brain, liver, and bone scans have been used only in those patients suspected of having extant disease." CT scanning is not mentioned at all.

The third edition of DiSaia's textbook published five years later in 1989 had identical recommendations for preoperative workup of early stage uterine adenocarcinoma patients, and the 4th edition (1997) differed only in that it mentioned that 75% of patients with endometrial cancer will present with stage I disease as well as noting that FIGO had adopted a new surgical staging system [3]. Preoperative use of CT scanning is not mentioned, but pelvic sonography is discussed at some length.

A decade later the 4th edition of another definitive gynecologic

oncology textbook-Practical Gynecologic Oncology by Berek and Hacker [4]-provided a more definitive preoperative workup than textbooks by other authors. For the first time authors divided the discussion of the topic into "routine" investigations and "non-routine" tests, the former listed in table form [4] in the text.

Specifically, these authors defined routine investigations as those which should be carried out on all patients with uterine cancer and included a full blood count, serum creatinine and electrolytes, liver function tests, blood sugar, urinalysis, and chest radiograph. Non-routine tests were only indicated for clinically advanced cases of uterine cancer. Sigmoidoscopy and cystoscopy were necessary only if bladder or rectal invasion was suspected on clinical examination or by history; and colonoscopy recommended only if patients had lower gastrointestinal symptoms or evidence of occult blood on digital examination. "Pelvic and abdominal computed tomography (CT scan) were indicated to delineate the extent of possible metastatic disease if patients present with any of the following circumstances: 1) abnormal liver function tests; 2) clinical hepatomegaly; 3) palpable upper abdominal mass; 4) palpable extra-uterine disease; or 5) clinical ascites [4]."

The authors noted that CT had limited usefulness in determining the extent of myometrial invasion because of the absence of a lateral view) or the presence of small disease in the retroperitoneal lymph nodes [5]. Interestingly, no mention was made of use of transvaginal sonography in the preoperative workup but MRI was rejected as a cost-effective method for preoperative evaluation patients with endometrial cancer because of its limited accuracy in evaluating para-aortic lymph nodes [6]. Lastly, elevated serum CA-125 levels were also mentioned, with the authors noting that elevated preoperative levels have been demonstrated to correlate with both advanced disease and positive lymph nodes [7]. Berek and Hacker's more nuanced approach to the preoperative workup of early stage uterine cancer patients by dividing this patient population into different categories depending on risk factors for occult metastatic disease was a real advance in clinical care of these patients. The shift away from a uniform "cookie-cutter" approach to patient management likely reflecting decades of accumulated surgical staging information on these patients.

The concept of the "high-risk" and "low-risk" uterine adenocarcinoma patient is now well-established in the gynecologic oncology literature as a methodology for identifying those patients with clinical early stage disease at greater risk for occult metastatic disease. The majority of the factors which can be used to identify such patients – involvement of the ectocervix, grade of the tumor, depth of invasion and size of the tumor, presence of extra-uterine

disease on physical examination – can ALL be obtained in the office during initial evaluation of the patient by careful pelvic examination, pap smear, endometrial biopsy, general physical exam, and possibly office transvaginal sonography.

2. Recent literature

Since the mid-1990s most of the literature on preoperative assessment of patients with uterine adenocarcinoma has focused on progressive refinements in changes in advanced imaging technologies (e.g., PET-CT, newer generation MRI machines, office-based pelvic sonography). There have also been occasional articles on the potential usefulness of preoperative serum CA-125 levels in predicting occult metastatic disease, and recent research into the identification of sentinel lymph nodes as an adjunct to surgery [8]. This latter modality will not be addressed in this article since it is an adjunct to surgical intervention at the time of or just prior to planned hysterectomy and staging. A discussion of the potential usefulness of routine advanced radiological testing and measurement of serum CA-125 in the preoperative workup of the early stage uterine adenocarcinoma patient follows.

3. Routine preoperative advanced radiological imaging in early stage uterine adenocarcinoma

Pelvic transvaginal ultrasonography, CT scans with or without contrast, MRI scanning, and PET- CT scanning might be obtained preoperatively in patients with clinical early stage endometrial adenocarcinoma primarily for two reasons: 1) to assess the depth of myometrial invasion and the size of the uterine cancer; and 2) to detect occult extra-uterine disease.

Within the past decade there have been significant improvements in CT scan spatial resolution, in the use of PET imaging as an adjunct to other diagnostic radiological tests, and in the development of contrast-enhanced MRI imaging. Despite the advances in ultrasound and CT scanning however, the current gynecologic cancer literature strongly suggests that neither modality remains accurate enough to precisely determine the depth of myometrial invasion [9], occult cervical invasion, or the presence of adnexal or nodal metastases [10].

Although improvements in MRI technology have improved this modality's ability to determine the depth of myometrial invasion and occult cervical invasion, with recent sensitivity and specificity of 90% or greater [11] the detection of small, occult nodal or adnexal metastases remains problematic.

Recent literature on use of 18F-fluorodeoxyglucose (18F-FDG)-PET/CT scans in early uterine cancer is sparse; evidence from the

gynecologic cancer literature on use of this modality in early stage (IB) cervical cancer has shown that 18F-FDG-PET/CT has a low sensitivity for detection of nodal metastases, and that routine use of this imaging modality in early stage cervical cancer had limited clinical impact in pretreatment planning for this disease [12].

There is no published literature to suggest that any currently available radiological imaging modality-ultrasound, CT, PET-CT, or MRI -is more accurate than intraoperative evaluation of the uterus, pelvis and abdomen with pathological analysis of operative specimens. This remains the gold standard. The most recent publication [13] on the accuracy of preoperative transvaginal sonography versus intra-operative frozen section in the assessment of myometrial invasion in endometrial cancer also clearly demonstrated that intraoperative frozen section – even though time consuming – is better than preoperative transvaginal sonography (TVS) in the assessment of myometrial invasion in determining whether to perform lymphadenectomy. If the standard practice in a particular institution or country is to perform full surgical staging on all patients with clinically early stage uterine adenocarcinoma, there is little reason (outside the research setting) to obtain either a transvaginal sonogram or intraoperative frozen section just to measure the depth of myometrial invasion.

4. Preoperative serum CA-125

The data on routine use of preoperative serum CA-125 levels in early stage uterine cancer all indicate that most patients with clinically early stage disease will have normal levels and that elevated levels consistently (but not always) predict occult metastatic disease; the former fact should not surprise since most patients with clinical stage I disease will in fact have disease surgically confined to the uterus. Based on this fact alone, routine use of preoperative serum CA-125 levels cannot be recommended as clinically or economically reasonable for every early stage uterine adenocarcinoma patient.

There is, however, substantial and sustained information in the gynecologic cancer literature which strongly suggests that preoperative serum CA-125 levels have meaningful, and occasionally statistically significant, value in predicting occult metastatic disease. Patients with clinical stage I uterine adenocarcinoma with lymphatic nodal metastases are 8.7 times more likely to have a preoperative serum CA-125 level above 40 U/mL than patients without nodal metastases [14], and in general patients with clinical stage I disease whose preoperative serum CA-125 levels are elevated are more likely to require lymphadenectomy [15]. Which cutoff level is ideal, however, remains a matter of some dispute.

Early work on CA-125 in uterine cancer in the late 1980s used an upper limit of 35 U/mL by convention since that was the value being used in the ovarian cancer clinical investigations for several decades. More recent work [16] has suggested that lowering the cutoff from 35 to 20 U/mL increased the ability of the preoperative CA-125 to predict the need for lymphadenectomy from 45% to 70% [17]. For these reasons there may be a role for preoperative serum CA-125 levels in those patients with clinical stage I disease who have a higher risk for metastatic disease, i.e., the “high-risk” early stage uterine adenocarcinoma patient. Because the majority of factors which make an early stage uterine cancer patient high risk are either known or determined at the time of initial evaluation, it is easy to obtain a serum sample to measure serum CA-125 at that time as well.

Discussion

Although employing advanced imaging techniques or measurement of serum CA-125 in the routine preoperative evaluation of the patient with clinical early stage uterine adenocarcinoma may occasionally reveal information about unexpected occult metastatic disease, this approach cannot be recommended on clinical grounds because of the relative lack of precision of information. Nor can routine use be recommended on economic grounds, because the testing is expensive and the diagnostic yield based on the available literature appears to be both inaccurate and predictably low. Were one to select one test – serum CA-125 or advanced imaging – on balance it would appear that the data would favor CA-125. But even this should not be the case for every early stage uterine adenocarcinoma patient. The take-home point appears to be that clinical early stage uterine cancer patients at low risk for metastatic disease almost always have normal serum CA-125 levels and unremarkable imaging, and should have neither serum CA-125 levels drawn nor advanced radiological imaging such as CT or MRI done outside of the research setting. The diagnostic yield on these tests is predictably too low, and their accuracy also too low, to justify their routine use in every low risk endometrial cancer patient once a patient has been identified as “low risk” by simpler testing-pap, endometrial biopsy, pelvic exam, and possibly office TVS-done in the office while surgery is being contemplated. Patients with early stage endometrial cancer who have factors which place them at higher risk for occult metastatic disease are the only patient sub-population that might benefit from additional preoperative diagnostic testing. High-risk factors include high

grade tumor (poorly differentiated cancers); high-risk histologies (papillary serous or clear cell cancers); pap smears demonstrating adenocarcinoma or atypical glandular cells with neoplastic features; clinical evidence of gross cervical involvement on pelvic examination; and/or deep invasion of the myometrium or large tumors if office ultrasound is available.

For these higher risk early stage patients the issue again becomes whether either preoperative Serum CA-125 or advanced imaging should be chosen, whether both should be done, or whether neither should be done. If the information provided by preoperative serum CA-125 or advanced radiological imaging is likely to change management, then they should be considered. But even if this is the case the usefulness of either modality will be a function of the planned surgical approach. For high-risk early stage endometrial cancer patients, some argument might be made that one or more of the tests should be performed, but if the plan is for all patients to have the same staging operation the main indication for radiological imaging would seem to detect that very rare patient who has unexpected large-volume metastatic disease (hepatic metastases, bulky supra-renal para-aortic lymph node involvement, extensive large-volume abdominal carcinomatosis) who would not be candidates for the standardized surgical operation and in whom the planned surgery would either be aborted or dramatically modified since the survival advantage for performing such operations is a matter of some dispute.

1. Possible lessons for Korea and the United States

In a country such as South Korea the medical care system for women with uterine cancer results in 90% or more of women being operated on at regional or university medical centers where virtually all undergo the same comprehensive surgical staging procedures (usually laparoscopic) after undergoing multiple radiological scans (TVS, CT, MRI) paid for by national health insurance. Under this set of circumstances the relative national uniformity of surgical care and preoperative evaluation provides a unique opportunity to determine the relative medical benefit and cost-effectiveness of the different components of a the pre- and intra-operative management of women with clinical early-stage uterine cancer.

In a system where every patient with clinically early-stage endometrial cancer is going to have individualized surgical staging, such as the United States, then the results of preoperative radiological evaluation, grade of cancer on endometrial biopsy, depth of invasion on office sonogram or preoperative MRI, pap smear results, pre-operative serum CA-125 are crucial because this in-

formation will be used to determine the extent of surgical staging at the time of hysterectomy. This is the case in much of the United States. On the other hand, in a system such as Korea's where the goal is for everyone to have the same surgical staging procedure regardless of the results of routine preoperative data on grade, pap, depth of invasion or tumor size etc then one of the main purposes of such preoperative testing has been eliminated.

Under this latter set of circumstances the primary reason for doing extensive radiological testing preoperatively is actually to detect the rare (5% or less) patient with metastatic disease that might preclude an otherwise uniform surgical resection and staging. In other words, scanning might be useful to allow the surgeon to plan to do less surgical staging than normal. However, given the relative rarity of finding a patient with clinical stage I uterine adenocarcinoma with abdominal carcinomatosis, occult liver metastases or bulky supra-renal para-aortic lymph nodes that might be detected and delineated on preoperative MRI, CT or PET-CT scanning, 95-98 out of every 100 such scans in this patient population would not affect the surgical management of the patient at all.

Outside of the clinical research setting then, it may be difficult to defend the routine use of such scanning in this patient population, particularly for the early stage uterine cancer patient known to be at low risk of having occult metastatic disease. Also, since many patients with abdominal carcinomatosis will have some evidence of extrauterine spread of disease on preoperative physical examination and the likelihood of successful debulking not accurately predictable by preoperative radiological imaging, and many patients with hepatic metastases will have abnormal liver function tests, the main focus of advanced radiological imaging in a patient with apparent early stage disease might actually come down to primarily detecting unexpected high-volume upper aortic retroperitoneal nodal disease.

Until all of these clinical questions are definitively resolved, ongoing active clinical investigations in Korea on the use of advanced radiological imaging techniques, and preoperative CA-125, in uterine cancer should continue, and when completed published. Their results could then be used to modify algorithms for preoperative patient evaluation.

Regardless of whether primary surgical therapy for clinically early uterine adenocarcinoma is individualized or standardized within a particular medical community however, in the long run the ultimate question/determination may well be an economic one. Which test, or combination of preoperative tests, is most likely to yield sufficient clinically useful information to the surgeon before surgery that will change intraoperative management.

In the low-risk clinical stage I patient, it would appear that only routine tests should be performed – complete blood count, chemistries, chest X-ray, pap smear, endometrial biopsy (grade of cancer), and possibly office ultrasound to assess uterine size and depth of invasion, along with a careful history and physical examination. Neither CA-125 nor radiological testing appears indicated either medically or economically in patients at low risk for metastatic disease.

In patients at higher risk for occult metastases, more testing such as CA-125 and CT, MRI, or PET-CT might be indicated but only if it will change the planned surgical therapy often enough, not rarely. Even in patients at higher risk for occult metastases the yield the expected yield and accuracy of these tests is limited, and the vast majority of such testing does not appear to provide useful information to the surgeon. At some point, the decision as to whether the government will continue pay for all of this preoperative radiological testing in early stage uterine adenocarcinoma patients may change.

One clinical question that awaits a definitive answer is a determination of whether those patients with clinical stage I uterine cancer with occult metastatic disease and elevated serum CA-125 levels have metastases in the same areas (adnexa or pelvic lymph nodes) that radiological testing will also likely detect. If this is the case, then CA-125 might be the preferred test since it is easier to perform and much less costly. Recent published large scale, cooperative data in the gynecologic oncology literature has clearly shown that the location of lymph node metastases is independently prognostic in those patients with metastatic disease confined to the retroperitoneal lymph nodes [18].

2. Caveats

It is important to keep in mind that the discussion in this paper has focused exclusively on a narrowly defined patient population – the patient with uterine adenocarcinoma for whom uterine preservation is not an issue and who has both disease clinically confined to the uterine corpus and who has adenocarcinoma by endometrial histology. For patients with more aggressive histological subtypes such as clear cell adenocarcinoma, papillary serous carcinoma, or uterine sarcoma, the recommendation in this paper likely do not apply and will be the subject of another paper. Similarly, for young women diagnosed with uterine adenocarcinoma for whom uterine conservation is being contemplated by their gynecologic oncologist, extensive radiological evaluation and serum CA-125 measurement may both be necessary even if the patient has apparent “low risk” endometrial adenocarcinoma. That too,

will be the subject of another review.

Acknowledgments

This article was presented at 16th Seoul International Symposium, Korean Society of Obstetrics and Gynecology, September 16, 2011.

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