Distinguished expert series

Role of lymphadenectomy in management of adenocarcinoma of the endometrium

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Summary

Purpose: To review the role of lymphadenectomy (LND) for patients with endometrial adenocarcinoma.

Methods: A review was undertaken of the English Language literature dealing with the role of LND for patients with endometrial adenocarcinoma (EC).

Results: The prognostic value of node status for EC patients has been recognized. LND performed by experienced surgeons has acceptable morbidity. Multiple series have suggested that significantly less external beam radiation is given to patients with known negative nodes. The decreased use of postop whole pelvic radiation has potential cost savings. However a survival advantage for LND has not yet been proven in a randomized clinical trials. United Kingdom investigators have begun a trial to determine if there is a demonstrable survival advantage for EC patients who undergo LND.

Conclusion: Although the morbidity, potential cost savings, and prognostic impact of node status are well accepted, it remains controversial as to whether LND provides a survival advantage. Trials are underway.

Key words: Surgical staging; Endometrial adenocarcinoma.

Introduction

The International Federation of Gynecology and Obstetrics (FIGO) declared in 1988 that adenocarcinoma of the endometrium (EC) should be surgically staged [1]. A surgical staging trial including hysterectomy, bilateral salpingo-oophorectomy, pelvic washings and selective pelvic and para-aortic node sampling was conducted by the Gynecologic Oncology Group (GOG). It established that approximately 22% of patients with clinical Stage I EC were "upstaged" including 11% that were found to have nodal metastases [2]. The risk of "upstaging" was a function of tumor grade, depth of invasion, lymphatic vascular space invasion (LVSI), and occult involvement of the cervix or adnexae [2, 3]. Although it is plausible that a more precise estimation of disease extent should facilitate optimal selection of adjuvant therapy for the individual patient, routine extended surgical staging (ESS) for EC has not been adopted by all.

Reservations expressed regarding the utility of ESS have included: 1) little additional information is gained beyond that acquired with close assessment of histological parameters of the uterus, cervix and adnexal specimen so that therapy is seldom altered, 2) increased morbidity, 3) cost considerations, and 4) the lack of level I evidence from a randomized controlled clinical trial (RCT) that the addition of ESS results in superior survival outcomes. Of course, proponents of ESS have countered that 1) fewer patients will undergo adjuvant therapy after ESS [4-7], 2) the morbidity is minimal [4, 8], 3) less adjuvant therapy can achieve significant cost savings [9], and that 4) survival rates are improved when ESS is done [10].

This review will examine the "Pros and Cons" of ESS for EC with regard to: 1) its impact on selection of adjuvant therapy, 2) morbidity, 3) cost considerations and 4) survival outcomes. It is recognized that a minimal requirement to undertake ESS for EC is an experienced surgeon and not all health care delivery systems may have a sufficient number of trained surgeons to provide ESS for all patients with EC nor do all patients have a body habitus or performance status which permits ESS.

Selection of Adjuvant Therapy

Those surgeons that promulgate *routine* ESS for EC base their recommendations on the GOG reports wherein nodal metastases were found in 11% of patients overall and as many as 35% of those with grade 3

and deep invasion to the outer-third of the myometrium had involved nodes [2, 3]. Adjuvant therapy can be recommended to patients with nodal metastases or other extrauterine disease [EUD]. ESS enables risk of recurrence to be further refined. Only 7% of those without EUD vs 43% of those with EUD developed recurrences [11]. Boronow *et al.* interpreted the GOG data as supportive of *selective node pelvic and para-aortic node sampling for those at substantial risk of nodal metastases* including those with vascular space invasion, extension to the cervix and adnexae, grade 3 lesions and any myometrial invasion, those with grade 2 lesions and at least mid-third invasion and those with outer-third invasion regardless of grade [3]. Subsequently others have promoted *routine* ESS as they believe it to have therapeutic value [10] or that ESS allows more limited use of external beam radiation therapy (ERT) [4, 6, 9, 12]. Progression-free survival rates in excess of 90% have been reported for EC patients with pathologically documented negative nodes who received limited intravaginal brachytherapy following ESS [13-15].

Those skeptical of the utility of ESS stress that 41% and 68% of those with positive pelvic and para-aortic nodes (PAN), respectively, had documented intraperitoneal or adnexal disease in the original GOG study [2] such that it is a *minority* of patients that are upstaged on the basis of positive nodes alone [16]. Furthermore, the original GOG study revealed if the adnexae and pelvic nodes were negative only 2% of patients had positive PAN [2]. Moreover recently, the stage distribution for 5,694 *surgically staged* patients determined that only 13% of patients were Stage III and of these only 26% were Stage III on the basis of nodal involvement such that a small minority of 3.5% of the whole population had Stage IIIC disease [17].

However the majority of patients that are evaluated for potential use of postoperative ERT are *not* those with advanced disease. Rather patients with apparent Stage I disease who have *not* undergone ESS are sent for consideration of ERT on the basis of uterine pathologic parameters. Gretz *et al.* reported that whole pelvic radiation was recommended 23% less often if nodes were known to be negative with outer-half invasion in grade 1 disease and 16% less often if known to be negative with outer-half invasion in grade 2 disease [7].

GOG 99 randomized *intermediate-risk* patients with EC after ESS to 50.4 Gy pelvic radiation versus no further therapy. The 2-year recurrence-free survival (RFS) was 97% after ERT vs 88% in the no further therapy arm [18]. There was an unappreciable effect on 2-year overall survival [18]. Following the 1998 presentation of GOG 99 at the Annual Meeting of the Society of Gynecologic Oncologists (SGO), Naumann *et al.* resurveyed 767 members of SGO (of whom 42% responded) and reported that except for grade 1 Stage IA disease significantly fewer recommended postop adjuvant therapy following ESS [5]. Twenty percent or greater decreases in recommendations for adjuvant radiotherapy were seen in the following groups of patients: grade 3 Stage IA and grade 2 Stage IB [5].

Survival rates may be improved in those patients with nodal metastases with the addition of cytotoxic chemotherapy to postoperative radiation [19-21]. Hicks *et al.* postulated that addition of chemotherapy should be considered given the disappointing 27% five-year disease-free survival in those with PAN metastases following ESS with external beam radiation 50.4 Gy to the pelvis and 45 Gy to the PAN [19]. Subsequently Onda *et al.* reported 75% survival in a series of 20 patients with PAN metastases treated with 50 Gy to the pelvis and PAN and three cycles of chemotherapy led to a 75% five-year survival rate [20]. Bristow *et al.* noted that the addition of chemotherapy to postoperative ERT for patients with nodal metastases led to a 0.22 hazard ratio for recurrence [21]. Larson *et al.* reported impressive results using systemic chemotherapy or hormonal therapy w/o any radiotherapy in a series of 15 patients with positive nodes wherein there were no failures after a median follow up of 51 months [22].

Although consensus is lacking as to what adjuvant therapy is best for patients with documented nodal metastases, it is apparent that those node-negative patients following ESS will be offered pelvic radiotherapy less frequently than those who have not undergone ESS.

Morbidity

It has been challenging especially in those who are morbidly obese to separate the surgical morbidity encumbered in performing the hysterectomy and adnexectomy from that associated with the node sampling. In an update of the original GOG report Morrow *et al.* documented a 19% complication rate following total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAHBSO) node sampling and a 0.3% mortality rate [23]. Single institution series have reported non statistically significant increases in operative times

and estimated blood losses after ESS compared to TAHBSO [8, 24]. Transfusion rates were 6% and 9.5% in Homesley *et al.'s* and Larson *et al.'s* series, respectively [8, 24]. A mean blood loss of 340 cc, a 1.5% rate of embolic events, and a 1.2% risk of lymphocysts after ESS was documented by Orr *et al.* [4]. However other series have noted an increase in vascular injuries, deep vein thromboses/emboli following node dissection [25, 26].

Investigators at the University of Washington have reported acceptable morbidity risks associated with ESS even in the morbidly obese patients [27]. They were able to accomplish lymph node dissection in 66% of those patients with body mass indices greater than 40. In that series only 13% of patients were transfused [27]. Given the safety of node sampling/dissection in the University of Washington series these investigators were strong supporters of its use given the challenges of palpating node abnormalities in such patients who often have large volume retroperitoneal fat [27]. Girardi *et al.* had previously documented that node palpation was not sufficiently sensitive in that 37% of nodal metastases were less than 2 mm and hence not amenable to detection by palpation [28].

The greater dissection involved with ESS might be expected to lead to more adhesions. Lewandowski *et al.* [29] and Corn *et al.* [30] have reported greater morbidity when ERT is given after ESS than when it is administered after simple TAHBSO. Lewandowski *et al.* documented enteric morbidity following radiation to 52 patients of whom 32 were status post ESS and 20 status post TAHBSO. They noted four complications severe enough to require subsequent laparotomy. All four were from the ESS group (12.5%) whereas none of those who received radiation post TAHBSO required surgical correction for enteric morbidity [29].

The proponents of ESS note that while radiation-induced enteric morbidity might be greater following ESS, fewer patients will be receiving external beam therapy [5-7] and hence the overall burden of enteric morbidity will decrease.

Cost Considerations

A decision analysis based on costs and charges from a single institution reported that the "average" woman gained about ten years of life from the hysterectomy portion of her therapy at a cost of 1,000 US dollars per life year gained and that adjuvant radiation therapy added on average one more year of life at a cost of 4,000 US dollars per life year gained [31]. The absence of randomized trials comparing ESS with *limited* ERT to TAHBSO and ERT based on uterine histological parameters has made it as yet impossible to determine which approach is most cost effective. The skeptics of ESS have pointed out that the models out there are retrospective in nature and do not account for the additional costs of complications incurred from radiation therapy after ESS [16]. However at least two institutions have reported data that suggested the more restrictive use of radiation therapy after ESS has potential to be cost saving [9, 12]. Barnes *et al.* claimed, based on a computerized model of charges incurred for 190 "hypothetical EC patients" managed with the three most prevalent clinical algorithms extant to treat EC, that *routine* ESS with adjuvant ERT limited to those with documented EUD yielded the lowest *charges* per patient of 12,778 US dollars [9]. The model employed by Barnes *et al.* calculated *charges* per patient of 15,997 US dollars if TAHBSO with node dissection based on depth of myometrial invasion and radiation therapy for uterine pathologic parameters and 17,343 US dollars if the algorithm employed TAHBSO with node sampling based on frozen section assessment of uterine histological factors [9]. Skeptics have charged that a single institution's *charges* may or may not reflect the costs incurred in providing the care. Horowitz et al reported a series of 144 grade 1 EC patients in which 71% had undergone ESS. Only 18 patients required adjuvant radiotherapy versus the 40 that would have been given adjuvant therapy if postoperative treatment recommendations had been based on uterine histological parameters alone [12]. They concluded "comprehensive staging should be considered in all patients with grade 1 tumors even with minimal uterine risk factors, since significant occult disease can be identified and adjuvant therapy can be appropriately tailored to reduce cost and morbidity from unnecessary radiation" [12]. However this series too was a single institution report and the costs per unit of surgery time and radiation therapy were not included in the abstract [12]. The question of cost considerations regarding *routine* ESS and more limited use of postoperative ERT versus the standard TAHBSO with ERT based on uterine histological parameters remains unanswered. Perhaps the Scottish verdict of "not proven" is most appropriate in this regard as what is assessed as "cost effective" in one health care system may not be the same in another health care system with a different cost structure.

Survival Outcomes

A randomized clinical trial comparing survival outcomes between the two surgical approaches of TAHBSO vs ESS has not yet been completed. It should be noted however that such a trial (MRC-ASTEC) has been accruing since 1999 in the United Kingdom under the direction of Dr. Harold Kitchener of St. Mary's Hospital in Manchester.

Multiple institutions have reported descriptive series wherein superior survival outcomes following ESS have been claimed [10, 32, 33]. The University of Alabama reported a series of 649 patients wherein multiple site, limited site and deferred node sampling was done in 212, 205 and 208 patients, respectively. In that series an *average* of 11 nodes were removed from those who underwent multi-site assessment versus only four from those who had limited node sampling [10]. Multi-site node assessment was associated with improved survival in the overall, high and low risk groups [10]. Chuang *et al.'s* series noted the risk of nodal recurrence fell from 8% in those without node sampling to 5% if less than three sites were sampled to 0% in those with at least three nodal sites were sampled [32]. He concluded "a selective approach to sampling that includes biopsy from both para-aortic and bilateral pelvic lymphatic zones appears to provide an accurate estimate of true node negativity" [32]. The Mayo Clinic reported a series with 137 high-risk patients (palpably enlarged nodes, > 50% depth of invasion or positive adnexae) and 51with documented nodal metastases [33]. Para-aortic node dissection (PAND) was defined in the mayo series as removal of a minimum of five nodes from the para-aortic region. Five-year overall survival improved from 71% in those without PAND to 85% in those who had undergone PAND [33]. Of the 51 patients with known nodal metastases the five-year overall survival was 42% in those without PAND versus 77% in those who had undergone PAND [33]. Nodal recurrences were documented in 37% of those w/o PAND but in none of those status post PAND. Mariani *et al.* concluded that the Mayo results "suggest a potential therapeutic role for formal PAND" [33].

In the absence of a mature randomized clinical trial comparing TABHSO to ESS, it is instructive to closely examine the results achieved in the two largest trials to date comparing postoperative external beam RT to no further therapy. GOG 99 included 390 patients that had undergone ESS with node sampling [all were node negative] and the PORTEC trial included 715 patients that had not undergone ESS [18, 34]. The dose of postoperative pelvic radiotherapy (ERT) was 46 Gy in the PORTEC trial and 50.4 Gy in GOG 99. Inclusion criteria were not identical in the two trials. GOG 99 allowed inclusion of patients with any grade as long as there was some evidence of invasion, whereas, the PORTEC trial mandated that grade 1 lesions have at least 50% depth of invasion, grade 2 any depth of invasion, and grade 3 have < 50% depth of invasion. Both of these trials noted the postoperative ERT improved local control but there was no appreciable improvement in overall survival in either trial [18, 34]. In the PORTEC trial the risk of loco-regional failure fell from 14% in the no further therapy arm to 4% following ERT, whereas, in the GOG trial the recurrence rate was 12% in the no further therapy arm and 3% in the ERT arm. There were only three pelvic/vaginal recurrences in the GOG 99 RT arm (two of which did not receive the prescribed ERT but were included in that arm as part of an intention-to-treat analysis) versus 18 in the no further therapy group [18]. These very similar local recurrence rates result in two series, one of which had undergone ESS and one which had not, do "beg the question" as to whether ESS improves disease control. Part of the challenge may be that the population included in GOG 99 was of sufficiently low risk that they were not likely to benefit from ESS, however another interpretation might be that the number of nodes removed was insufficient to improve local control. There is *not* within the GOG a "defined number of nodes" which must be included in node sampling specimens. Rather the GOG procedure manual describes that in pelvic node sampling enlarged or suspicious nodes should be excised or biopsied if unresectable and that nodal tissues should be removed from the 1) distal half of each common iliac artery, 2) anterior and medial aspect of the proximal half of the external iliac artery and vein and the 3) distal half of the obturator fat pad. A PAN sampling should include excision of enlarged or suspicious nodes; on the right it should remove nodal tissue over the distal vena cava from the inferior mesenteric artery to the mid common iliac artery and on the left the tissue between the aorta and left ureter from the inferior mesenteric artery to the left mid common iliac artery.

Another potential benefit of node sampling would be to identify those that require adjuvant therapy of a nature to address their risk of distant failure. Unfortunately again mature randomized clinical trials do not exist wherein the sole difference between the two arms is the extent of node sampling/dissection. The best that surgical-clinicians can do is to examine the evidence that is extant from previously conducted trials and descriptive series.

Lymphadenectomy appears to lower the risk of nodal failure [32, 33], however isolated nodal failure is rare in endometrial cancer. In the PORTEC series wherein *none* of the patients underwent ESS those that were randomized to the no ERT arm suffered more local recurrences but 73% of those had a vaginal component. Only ten of the 360 (2.7%) evaluable patients in the TAHBSO no ERT arm of the PORTEC study suffered isolated pelvic recurrences [34].

Those single institution series that claim therapeutic effect for lymphadenectomy [10, 33] may be alternatively interpreted that identification of nodal metastases via ESS allows for identification of those patients most in need of adjuvant therapy but may not be therapeutic. The GOG staging data noted a recurrence rate of 35% in the 57 of patients who had undergone ERT following ESS but the survival rate was > 90% in those who had not received ERT [11].

The observation that all patients do better after a node sampling may be construed as a surgical "Will Rogers effect" and reflective of the phenomenon of *stage migration.* It is equally, if not more, plausible that the removal of some number [not yet defined how many is enough] of negative nodes *identifies* those destined to do well because they never had node metastases as it is to say that removal of *negative* nodal tissue improved survival. This does have the benefit of allowing the clinician to limit the use of adjuvant therapy to those most in need but it should not be construed that removal of the negative nodes is what improved survival. In the GOG series 11% (23/222) of patients were identified as having positive pelvic nodes [11]. Of those 23 patients with pelvic node metastases, 12 (57%) suffered distant recurrences whereas only 15/199 (7.5%) with uninvolved nodes suffered distant metastases [11]. The most biologically plausible "construct" of this recurrence data would be that identification of nodal metastases is prognostic. If lymphadenectomy is therapeutic then the risk of distant recurrence should be lower in patients who have nodal metastases resected and adjuvant therapy directed to the involved field, but in fact the risk of distant recurrence remains sufficiently high so that systemic therapy has been promoted for those with positive nodes [19, 20, 22]. In fact GOG 122 found a progression-free survival and overall survival hazard ratio of 0.67-0.68 in favor of systemic multi-agent cytotoxic therapy for patients with Stage III-IV EC [35].

Another way to examine whether ESS lymph node sampling/dissection might be therapeutic is to examine the distant failure rates described in GOG 99 [18] wherein all the patients had ESS relative to those seen in the PORTEC trial [34] wherein none of the patients underwent ESS. It should be recalled that while grade 3 lesions represented 18% and 10% of those enrolled in the GOG and PORTEC trial respectively, only 17% of those in the GOG trial had outer third invasion versus outer half invasion in 59% of those in the PORTEC study. There were 6.4% distant recurrences in the no radiotherapy arm of GOG 99 versus 7% in the PORTEC trial [18,34]. The risk of distant recurrence was 5.2% in the GOG 99 ERT arm and 7% in the PORTEC ERT group. So while such a comparison is not as ideal as a randomized trial between ESS and TAHBSO it does suggest that impact on distant recurrences will be small and a randomized trial will require thousands of patients if we are going to "prove" a therapeutic benefit for progression-free or overall survival.

Conclusions

Single and multi-institutional studies support that lymph node sampling/lymphadenectomy for EC can be done with acceptable morbidity in experienced hands [2, 4, 8] and that the findings will definitely decrease the number of patients who will be offered postoperative external beam radiotherapy [5-7, 13, 22]. Single institution series suggest that by limiting the number of patients requiring postoperative ERT, ESS can save health care dollars [9, 12]. The data that ESS with node sampling/lymphadenectomy can decrease nodal recurrences has been reported in two series [32, 33]. However the data is less convincing that ESS is therapeutic or improves survival. Rather a stronger case can be made that the findings from ESS can identify those patients most in need of adjuvant therapy as they have increased risk to suffer subsequent recurrences more than half of which will be distant recurrences suggesting that the radiotherapy alone for nodal metastases may not be sufficient [11].

While the Society of Gynecologic Oncologists remains committed to ESS for EC, it must be recognized that not all patients with EC will undergo surgery by SGO members, not all patients will have a body habitus or general medical condition that permits ESS, and that excellent results have been achieved in large series without ESS [34]. In fact the GOG has completed a randomized clinical trial (GOG 122) comparing whole abdominal radiation to combination cytotoxic therapy for advanced Stage III and IV disease wherein lymph

node sampling was *optional*. Of the 388 evaluable patients in GOG 122, 24% of the patients did not have para-aortic nodes sampled and 15% did not have pelvic node sampling [35]. Currently the GOG is conducting another advanced stage trial (GOG 184) wherein node sampling is optional and all patients receive radiotherapy to a field recognized to be at risk but then are randomized to a cytotoxic regimen of cisplatin plus doxorubicin with or without paclitaxel. These recently completed and ongoing trials emphasize the *"reality"* that clinical investigation will continue and that relevant important questions can be asked of EC cancer patient populations who have not undergone node dissection. We should continue this work and commend the MRC-ASTEC investigators in the United Kingdom who are undertaking the seminal trial that may be able to answer whether or not node dissection for EC is therapeutic or only prognostic [36].

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