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Controversies Regarding the Utility of Lymphadenectomy in Endometrial Cancer

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1. Introduction

The value of lymphadenectomy (LND) in the management of endometrial cancer remains controversial. Although it is required for the surgical staging of the disease (FIGO 2009) and its prognostic value is indisputable, its therapeutic benefit remains a matter of debate. Furthermore, systematic pelvic (PLND) and para-aortic lymphadenectomy (PaLND) cause morbidity, even when performed using minimally invasive surgical techniques. A reliable means of sentinel lymph node (SLN) mapping may be the way forward. In this chapter we review the literature surrounding this topic, identify areas for research and suggest a pragmatic approach to managing this dilemma.

2. Overview

The lifetime risk of a woman in the United States to develop uterine cancer is 2.5%. It is the fourth most common cancer in women and accounts for 6% of all female cancers and 3% of cancer-related deaths (Jemal et al., 2010). Two different clinico-pathological subtypes of endometrial cancer are recognized: Type I, which is endometrioid and estrogen-related, and Type II, which is non-endometrioid and non-estrogen-related.

When the disease is confined to the uterus, a hysterectomy and bilateral salpingo-oophorectomy would constitute adequate treatment. If the disease has spread outside the uterus, adjuvant treatment is required to maximize the potential for cure. At the time of diagnosis approximately 85% of endometrioid cancers are confined to the uterine corpus and are therefore associated with a favorable five-year survival rate of 83% (Creasman et al., 2006). In the Western world at least 85% of newly diagnosed endometrial cancers are endometrioid in type (Amant et al., 2005; Creasman et al., 2006). As the propensity for lymph node metastasis in these patients can vary from clinically negligible to 20%, depending on the grade and stage of presentation, management of this subtype is fraught with ambiguity. In non-endometrioid cancers, 35% have already spread beyond the uterine corpus at presentation. Among the non-endometrioid uterine cancers, clear cell and papillary serous cancers are the worst offenders, with extra-uterine metastasis occurring in 33% and 41% of cases, respectively, which is reflected in correspondingly low five-year survival rates of 63% and 53%, respectively (Creasman et al., 2006).

Following primary surgical treatment, adjuvant treatment is tailored according to the risk of lymph node metastasis and recurrent disease. The current method of risk stratification uses

patient-related factors as well as the definitive pathological findings identified to be associated with increased risk of lymph node metastasis and recurrence to group patients into low-, intermediate- and high-risk categories. Other determinate factors are age, tumor grade, non-endometrioid subtype and extension of the disease, including depth of myometrial invasion and lymphovascular space invasion (LVSI) (Creasman et al., 1987; Kadar et al., 1992; Keys et al., 2004; Morrow et al., 1991).

Risk group			Risk of metastatic LN (%)	Risk of recurrence at 5 years (%)
Low		Ia, Grade I & II	<3	<5
Intermediate	Low	others	3-5	10-15
Risk factors (RF): age, grade III, LVSI present, deep myometrial invasion (>50%)	High	≥70 years + 1 RF ≥50 years + 2 RF any age with 3 RF	10-30	20-25
High		Stage II-IV, non-endometrioid uterine cancers	>30	>25

Table 1. Classification of endometrial cancers adjusted to FIGO 2009.

The disadvantage of this system is that lymph node metastasis is presumed rather than known for certain, and a proportion of patients will be over-treated with adjuvant treatment. Furthermore, if removal of the affected nodes has a therapeutic value, and evidence suggests it has (please refer to section 6), patients would miss out on the survival advantage conferred by a systematic lymphadenectomy. Having access to information about lymph node status pre-operatively would allow surgery to be tailored accordingly. Below, we discuss the currently available methods for pre-operative assessment of the spread of disease.

3. Pre-operative assessment of the spread of disease

3.1 CA 125

Four studies have evaluated the role of CA 125 in evaluation of patients with endometrial cancer. All four conclude that a high CA 125 cut-off, ranging from 20 to 40U/ml., is an independent risk factor for extra-uterine disease or lymph node metastasis. Nevertheless, its sensitivity and specificity are only around 80% (Chung et al., 2006; Han et al., 2010; Hsieh et al., 2002; Sood et al., 1997). This means that 1 in 5 patients will be over-treated and 1 in 5 undertreated.

3.2 Imaging

3.2.1 Ultrasound

Most patients with endometrial cancer will have a transvaginal ultrasound (TVS) as it is the imaging procedure of choice to assess post-menopausal bleeding, the most common presenting symptom. TVS is a non-invasive, readily available and inexpensive test that has a very high sensitivity of 96% for raising suspicion about the presence of endometrial cancer

when using a cut-off of ≥5mm endometrial thickness. Its specificity varies between 61% and 81% for all endometrial diseases (Fleischer, 1997; Smith-Bindman et al., 1998). False-negative rates have been reported at around 1% and are due to adenomyosis or distortion of the endometrial lining by fibroids (Smith-Bindman et al., 1998). If morphologic features such as endometrial heterogeneity were added to endometrial thickness, then specificity and the false-negative rate might be improved (Dubinsky, 2004).

After the diagnosis of endometrial cancer is made, TVS could provide information about the depth of myometrial invasion. Loubeyre et al. (2011) reviewed the correlation between the depth of myometrial invasion on TVS and the final pathology in eight studies with a total of 605 patients with endometrial cancer. They found the sensitivity to be 80% (range 58% to 95%) and so too the specificity (range 71% to 92%). Evaluation of cervical involvement by TVS is less informative, with sensitivities varying between 54% and 88% and specificity between 87% and 100% (Celik et al., 2010; Lee et al., 2011; Loubeyre et al., 2011).

The weaknesses of TVS are that it is operator-dependent and lymph nodes cannot be properly evaluated.

3.2.2 CT

CT scan is considered inferior to TVS in determining the depth of myometrial invasion (accuracy around 60%). The ability of CT scan to identify cervical involvement has not been properly investigated. The value of multidetector CT in the staging of endometrial cancer has yet to be explored (Lee et al., 2011; Loubeyre et al., 2011). Using a 1cm cut-off to evaluate pelvic and para-aortic lymph nodes, the sensitivity of CT is only 50% (range 44% to 66%)—no better than flipping a coin; its specificity is 95% (range 73% to 98%) (Lee et al., 2011). This poor correlation is due to the fact that only 39% of metastatic lymph nodes are enlarged and 37% are smaller than 2mm (Creasman et al., 1987; Mariani et al., 2000). For the same reason, MRI and PET-CT have similar results in detecting metastatic lymph nodes.

3.2.3 MRI

The imaging procedure of choice to assess patients with endometrial cancer is MRI, but it is an expensive test and, as mentioned before, is ineffective in detecting metastatic lymph nodes. However, MRI is superior to TVS and CT in evaluating the depth of myometrial invasion as well as cervical involvement (Loubreyre et al., 2011; Lee et al., 2011, on behalf of the American College of Radiology). Loubeyre et al. (2011) reviewed the correlation between depth of myometrial invasion on MRI and final pathology in nine studies with a total of 1,115 patients with endometrial cancer. Sensitivity ranged from 56% to 88% and specificity from 74% to 100%. This group also reviewed the correlation between cervical involvement on MRI and final pathology in five studies with a total of 623 patients with endometrial cancer. Sensitivity ranged from 47% to 72% and specificity from 83% to 100%. In its pre-treatment evaluation of endometrial cancer, the American College of Radiology indicates that the accuracy of MRI in predicting myometrial involvement ranges from 85% to 92%, cervical involvement from 86% to 95% and overall staging from 85% to 93% (Lee et al., 2011).

3.2.4 PET

The role of PET in endometrial cancer is more in the detection of disease recurrence than in the pre-operative evaluation of extra-uterine disease (Lee et al., 2011).

4. Pre-operative assessment of grade and histological subtype of the disease

4.1 Pathology

In addition to a TVS, a patient with post-menopausal bleeding needs a tissue diagnosis. This can be done by pipelle biopsy (office endometrial biopsy) or dilatation and curettage (D&C). The sensitivity of pipelle biopsy in detecting endometrial cancer is 99.6%. The sensitivity of D&C is similar; it serves as the diagnostic procedure when pipelle biopsy is not feasible or is inadequate (Dijkhuizen et al., 2000). After the diagnosis of endometrial cancer is made, pre-operative assessment of the aggressiveness of the disease is very important to tailor the surgery. Patients with a high-grade endometrial cancer have a 15% to 20% risk of having metastatic lymph nodes (Creasman et al., 1987). Therefore, the ability to grade the tumor accurately on the diagnostic sample, be it a pipelle biopsy or a D&C, is crucial.

A D&C reflects the final FIGO grade more accurately than a pipelle biopsy. Leitao et al., (2009) reported a higher grade at the time of hysterectomy in 8.7% of patients when the diagnosis was made with a D&C, compared to 17.4% with a pipelle biopsy. Obermaier et al. (1999) found that 20% of Grade 1 endometrial cancers on D&C were upgraded to Grade 2 (or Grade 3 in 2% to 3% of cases) while 4% were downgraded at final pathology. In summary, pre-operative FIGO Grade 1 endometrioid endometrial cancer correlates in 80% to 85% of cases with the grade on the final hysterectomy specimen. The difference between pipelle biopsy and D&C does not warrant extra anesthesia. Changing from the three-grade FIGO system to a binary system does not improve accuracy sufficiently to warrant replacing the FIGO system, which is currently in use worldwide. However, molecular tests may have greater potential to support the binary system in the future (Clarke & Gilks, 2010). In a review of Stage III cases treated at our institution, we found that less than half were suspected preoperatively (Denschlag et al., 2007). A recent French multicentre study on sentinel lymph node mapping, found that 29% of tumors thought to be grade 1 preoperatively or intraoperatively, were upgraded to grade 2 or 3 or at final histology and 7% of patients thought to have type I tumors had type 2 endometrial cancer at definitive histology (Ballester et all 2010).

4.2 Conclusion

Identifying metastatic lymph nodes by currently available imaging techniques is only as sensitive as flipping a coin (50%). Assessing risk factors for metastatic lymph nodes, such as depth of myometrial invasion and cervical involvement, is most accurate with MRI, reaching at least 85% (in study circumstances) for both risk factors. Pre-operative assessment of Grade 1 tumors correlates with the final grade in 80% to 85% of cases.

This means that approximately one patient in five is underestimated pre-operatively for risk factors that include depth of myometrial invasion and/or cervical involvement and/or tumor grade. Consequently, tailoring surgery based on pre-operative assessment alone is not adequate.

5. Intra-operative assessment

5.1 Palpation of lymph nodes

Intra-operative palpation of pelvic or para-aortic lymph nodes will reveal only 39% of the metastatic lymph nodes (Mariani et al., 2000). Creasman et al. (1987) have already shown that 37% of metastatic lymph nodes are smaller than 2mm. So neither pre-operative imaging nor intra-operative palpation is accurate enough to dispense with surgical excision.

5.2 Gross inspection

Assessment of the depth of myometrial invasion of an endometrial cancer by gross visual examination has been studied in three prospective studies (ranging from 148 to 403 patients). Compared to definite hystopathological findings, sensitivity varies from 71% to 79% and specificity from 93% to 96%. Evaluation of cervical involvement by gross inspection has never been studied (Loubreyre et al., 2011).

5.3 Frozen section

Given our inability to predict lymph node metastasis pre-operatively with accuracy, can intra-operative frozen section analysis help determine which patients should have a systematic PLND and PaLND? The literature on this is conflicting.

Correlations of 58% to 96% for grade with intra-operative frozen section analysis and final pathologic results have been reported. A similar variation is reported in the accuracy of intra-operative section analysis of depth of myometrial invasion (72% to 95%) as well as of cervical involvement (66% to 97%) (Frumovitz et al., 2004; Loubeyre et al., 2011).

Several retrospective studies, which used a combination of risk factors (grade and depth of myometrial invasion, histological subtype) to compare intra-operative frozen section analysis and final pathologic results, found that the correlation was not sufficient to dispense with surgical staging (Frumovitz et al., 2004; Denschlag et al., 2007; Papadia et al., 2009). According to Papadia et al., 78% of patients undergo appropriate surgery, while 16% are under-staged and 6% over-staged.

5.4 Adding tumor size

In an attempt to increase the accuracy of frozen section analysis, several investigators have studied the benefit of factoring in tumor size as determined intraoperatively. In 1987 Schink et al. described that patients with clinical Stage 1 endometrial cancer had only a 4% risk of lymph node metastasis if their endometrial cancer was ≤2cm. The Mayo Clinic in Rochester, Minnesota, uses a thorough intra-operative frozen section to identify a sub-group of patients with endometrioid adenocarcinoma in whom the risk of lymph node metastasis is negligible and who therefore do not warrant lymphadenectomy. The characteristics are: Type I, Grades 1 and 2; myometrial invasion less than 50%; primary tumor diameter less than 2cm, (Mariani et al. 2008).

The concept of adding tumor size to improve the ability of frozen section to correctly identify low-risk patients was evaluated by Yanazume et al. (2011) in a retrospective study of 228 patients. They used tumor size of ≤3cm as their cut off. This study found that a Grade 1 or 2 endometrial cancer, with a tumor diameter of ≤3cm and ≤50% myometrial invasion, accurately predicts the absence of lymph node metastasis.

5.5 Conclusion

The palpation of lymph nodes during a laparotomy should not be used to determine the need for a systematic PLND and PaLND. Frozen section analysis is useful to distinguish a benign from a malignant lesion, but it has limitations with regard to time involvement, inadequate sampling (only part of the tumor) and the technique of rapid freezing itself. However, despite these constraints, a detailed and thorough intra-operative frozen section that assesses subtype, grade, myometrial invasion and tumor size is preferable to the alternatives, namely, that of an unnecessary lymphadenectomy with its attendant complications in low risk patients, or not carrying out a systematic lymphadenectomy in patients at high risk of lymph node metastasis.

6. Surgical staging

As discussed in the previous section, it is clear that surgical staging and knowledge of lymph node status plays a very important role in the management of patients with endometrial cancer. What is not clear is what constitutes an adequate LND. The practice varies from selective sampling of accessible nodes to systematic LND. Is the latter necessary? Is a PLND adequate or is a PaLND required in addition to a PLND? If a PaLND is required, what are the limits of dissection? What are the additional risks of a LND? When are these additional risks justified? Does LND have a therapeutic effect? Below, we discuss the studies that have tried to address these questions.

6.1 Definitions

For a systematic PLND, all lymph nodes and fatty tissue between the external and internal iliac arteries, from the bifurcation of the common iliac artery up to the circumflex vein and above the obturator nerve, should be removed. A systematic PaLND includes resection of all lymph nodes and fatty tissue overlying the common iliac artery, vena cava and aorta anteriorly up to the renal vessels and extending laterally to the edge of the psoas major muscle.

6.2 The randomized controlled trials on lymphadenectomy

To date, two randomized controlled trials (Benedetti Panici et al. in 2008 and the MRC ASTEC trial 2009) have investigated whether the addition of PLND to standard hysterectomy with bilateral salpingo-oophorectomy improved overall survival and disease-free survival in patients with preoperative Stage I endometrial cancer.

6.2.1 Benedetti Panici et al., 2008

In this Italian RCT, the role of systemic PLND or no PLND in early-stage endometrioid or adenosquamous endometrial cancer (FIGO 1988) was examined. Patients with Stages IA and IB Grade I, were excluded; 514 patients were randomized to undergo PLND (n=264) or not (n=250). A minimum of 22 PLNs were removed; median was 30. PaLND and adjuvant radiotherapy were left to the discretion of the treating physician; 26% in the PLND group had PaLND compared to 2% in the no-PLND group; the median number of PaLN's removed in the LND group was four. The proportion of patients who received adjuvant radiotherapy was similar in both groups: ±31-35%. At a median follow-up time of 49 months, no difference in the disease-free or overall survival rates was seen between the two groups. The estimated blood loss and the number of intra-operative complications were similar in both arms, but operating time and hospital stay were longer in the PLND group. Furthermore, more post-operative complications were noted in the PLND group, predominantly due to the formation of lymphocysts and lymphedema (35 versus 4). The PLND group was diagnosed with 13% metastatic LN versus only 3% in the no-PLND group. The authors concluded that although disease-free or overall survival is not improved, a systemic PLND significantly improved surgical staging.

6.2.2 ASTEC Trial, 2009

Eighty-five centers in four countries participated in the ASTEC Trial, randomizing 1,408 women with histologically proven endometrial cancer that was pre-operatively (clinically) thought to be confined to the uterus (despite PLN enlargement on CT or MRI), to standard

surgery with or without systemic PLND. At a median follow-up time of 37 months there was no difference in disease-free or overall survival in both groups. According to the authors, PLND cannot be recommended as a routine procedure for therapeutic purposes outside of clinical trials.

However, the ASTEC Trial had several serious shortcomings:

- 20% of patients in the systemic PLND group had ≤4 nodes removed; only 40% of the patients in the systemic PLND group had >14 PLN harvested.
- Furthermore, about half the cases were well-differentiated Stage IA or IB, where the risk of nodal metastasis is 3% to 5%.
- In a large prospective RCT, risk factors tend to be equalized in the two arms. Nevertheless, the PLND group had 3% more poor histotypes, 3% more Grade 3 lesions, 3% more LVSI and 10% more deep myometrial invasion. Although these are minor variances, in large groups this could influence small differences.
- Patients were randomized to receive adjuvant therapy regardless of node status.

6.3 Observational studies on the effect of lymphadenectomy on survival

6.3.1 Cragun et al., 2005

In a retrospective analysis of 509 patients, Cragun et al. (2005) noted that patients with poorly differentiated cancers having more than 11 pelvic nodes removed had improved overall survival (hazard ratio [HR] 0.25; P < .0001) and progression-free survival (HR 0.26; P < .0001) compared with patients having poorly differentiated cancers with 11 or fewer nodes removed. Among patients with cancers of Grades 1 to 2, the number of nodes removed was not predictive of survival. In multivariate analysis, a more extensive node resection remained a significant prognostic factor for improved survival in intermediate-/high-risk patients after adjusting for other factors including age, year of diagnosis, stage, grade, adjuvant radiotherapy and the presence of positive nodes (P < .001). Performance of *selective* PaLND was not associated with survival.

6.3.2 Chan et al., 2006

Further evidence for the prognostic and therapeutic benefits for a thorough LND came from Chan et al., who used the United States National Cancer Institute's Surveillance, Epidemiology and End Results Program dataset of 39,396 women with endometrioid uterine cancer. They compared 12,333 patients who underwent surgical-staging procedures, including LND, with 27,063 patients who did not receive a LND to determine the potential therapeutic role of LND in women with endometrioid corpus cancer. They found that the five-year disease-specific survival was significantly improved by lymphadenectomy, and that with increasingly high-risk disease, the survival advantage conferred by LND was progressively greater. The five-year disease-specific survival for Stages I, II, III and IV patients who underwent LND was 95.5%, 90.4%, 73.8% and 53.3%, respectively, compared with 96.6%, 82.2%, 63.1% and 26.9% for those who did not (P > 0.05 for Stage I, P < 0.001 for Stages II to IV). In the subset of patients with Stage I, Grade 3 disease, those who underwent LND, had a better disease-specific survival than those who did not (90% versus 85%; P 1⁄4 0.0001). However, no benefit for LND was identified for patients with Stage I, Grade 1 (P 1⁄4 0.26) and Grade 2 (P 1⁄4 0.14) disease.

The group also used the data from the 12,333 patients who underwent LND to determine whether the node count or extent of the LND had a therapeutic benefit, and they found that

it did in women with intermediate-/high-risk endometrioid cancer but not those with low-risk endometrial cancer. In the intermediate-/high-risk patients (Stage IB, Grade 3; Stages IC and II to IV, all grades), a more extensive lymph node resection (1, 2-5, 6-10, 11-20, and >20) was associated with improved five-year disease-specific survivals across all five groups at 75.3%, 81.5%, 84.1%, 85.3% and 86.8%, respectively (P < .001). For Stage IIIC to IV patients with nodal disease, the extent of node resection significantly improved survival from 51.0%, 53.0%, 53.0% and 60.0%, to 72.0%, (P <.001). However, no significant benefit of lymph node resection in low-risk patients could be demonstrated (Stage IA, all grades; Stage IB, Grade 1 and 2 disease; P ¼ 0.23). In multivariate analysis, a more extensive node resection remained a significant prognostic factor for improved survival in intermediate-/high-risk patients after adjusting for other factors, including age, year of diagnosis, stage, grade, adjuvant radiotherapy and the presence of positive nodes (P <.001). In a follow-through study on 11,443 patients, Chan et al. (2007) investigated the association between the number of lymph nodes examined and the probability of detecting at least a single lymph node involved by metastatic disease in patients with endometrioid corpus cancer to define what constitutes an adequate LND. Their results suggest that the ideal node count is 21 to 25 lymph nodes. Although these are retrospective analyses, the strength of the data lies in the size of the sample and the fact that the study population reflects real-life practices across a range of units from community hospitals to tertiary-care academic centers. The limitations include the lack of detail regarding the location and size of the lymph nodes resected, specifically on what the contribution of PaLND is to the sample.

6.3.3 Para-aortic lymphadenectomy

There is evidence that patients with high-intermediate and high-risk endometrial cancer have 10% to 25% risk of metastatic PaLN (Kadar et al., 1992; Keys et al., 2004; Morrow et al., 1991). About 50% of patients with metastatic PLN have metastasis in the PaLN (Mariani et al., 2008; Watari et al., 2005). Sixteen percent of patients with high-risk endometrial cancer have metastasis only to the PaLN and not to the PLN (Mariani et al., 2008) and 77% of patients with para-aortic metastases harbor disease above the inferior mesenteric artery. It would appear that PaLND, when indicated, should be systematic and extend to the renal vessels. Although Abu-Rustum et al. (2009) reported that in their patients only 1% had isolated para-arotic metastasis (with negative pelvic nodes), they used a count of eight pelvic nodes as indicating a satisfactory pelvic lymphadenectomy and the retrieval of one para-arotic lymph node below the inferior mesenteric artery as evidence of a PaLND. Most gynecologic oncologists consider these LN counts inadequate to make firm conclusions.

6.3.4 SEPAL study 2010

Given the discordance between the findings of the large observational studies (Cragun 2005, Chan 2006, 2007a, 2007b) indicating a significant advantage in survival conferred by an extensive lymphadenectomy, and the RCTs indicating otherwise, Yukiharu Todo and colleagues investigated whether it was the addition of PaLND that improved survival in endometrial cancer (SEPAL). They studied cohorts from two tertiary-care gynecologic oncology units in the city of Sapporo, Japan. Although their study is retrospective, bias was kept to a minimum as the centers differed in the use of PaLND, which was practiced as a routine standard of care in one center and not in the other. The cohorts from both centers

had systematic PLND; median pelvic lymph node count 34 (21 to 42) in the PLND group (325 patients) versus 59 (46 to 73) in the PLND and PaLND group (n=346). The number of PaLN counts in the two groups were 0 versus 23 (16 to 30). Patients at intermediate or high risk of recurrence were offered adjuvant radiotherapy or chemotherapy. Overall survival was significantly longer in the PLND and PaLND group than in the PLND group (HR 0.53, 95% CI 0.38 to 0.76; p=0.0005). This association was noted in 407 patients at intermediate or high risk (p=0.0009), but not in low-risk patients. Multivariate analysis of prognostic factors showed that in patients with intermediate or high risk of recurrence, PLND and PaLND reduced the risk of death compared with PLND (0.44, 0.30 to 0.64; p<0.0001). Analysis of 328 patients with intermediate or high risk who were treated with adjuvant radiotherapy or chemotherapy showed that patient survival improved with PLND and PaLND (0.48, 0.29 to 0.83; p=0.0049) and with adjuvant chemotherapy (0.59, 0.37 to 1.00; p=0.0465) independently of one another. The authors concluded that combined PLND and PaLND is recommended as treatment for patients with endometrial carcinoma of intermediate or high risk of recurrence.

6.4 Caveat with lymph node counts

Although there is much debate on constitutes the optimum pathological sampling of pelvic lymph nodes in endometrial cancer, the importance of counting the number of lymph nodes detectable in the pathologic specimens is incontrovertible (Berney et al., 2010). Weingärtner et al. (1996) reported on the average number of PLNs found at the time of autopsy. In 30 human cadavers (19 males and 11 females, mean age of death 64 years), it was found that there were 22.7±10.2 lymph nodes (ranging from 8 to 56) in the pelvis. It has been clearly established that lymph nodes undergo fatty involution that increases with age (>72 years), BMI (>27.8), diabetes, hypothyroidism and previous chemotherapy. A recent study confirmed this phenomenon for superficial lymph nodes in the cervical, axillary and inguinal regions. The fatty degeneration of lymph nodes makes their identification unreliable with either imaging or palpation at the time of surgery or during gross pathologic examination (Arango et al., 2000; Giovagnorio et al., 2005). Consequently, the value of lymph node counts in the elderly and in obese women with endometrial cancer is highly dependent on the thoroughness of the pathology technician.

6.5 Conclusion

In summary, it is clear that patients who have low-grade endometrioid adenocarcinoma with minimal myometrial invasion have very low risk of lymph node metastasis and do not benefit from a LND. Patients at risk of lymph node metastasis require a systematic PLND as well as PaLND. The latter should extend up to the renal vessels.

7. Morbidity of lymphadenectomy and benefits of minimally invasive approach

One of the factors that precludes LND in patients with endometrial cancer is the morbidity associated with an LND. Given that the risk factors for endometrial cancer are old age, diabetes, hypertension and obesity, it follows that a substantial number of women diagnosed with endometrial cancer have these co-morbidities, thus making them high risk for prolonged and technically complicated surgery. Several studies have tried to assess the

additional risks posed by a systematic LND and the benefits of performing the surgery by laparoscopy or robotic surgery.

In a large retrospective study, Cragun et al. (2005) summarized the morbidities of LND by laparotomy. Two to three percent of patients had small bowel obstruction or ileus, deep vein thrombosis and lymphocysts requiring drainage. Patients undergoing PLND and PaLND required longer anesthesia time and hospital stay and had greater blood loss compared to those who had PLND alone. Up to 8% of patients had a wound infection. Chronic lymphedema of the lower limbs was observed in 2.5% (Abu-Rustum et al., 2006).

Querleu et al. (2006) audited 1,000 patients who had a *laparoscopic LND*. Only 1.3% were converted to laparotomy. Intra- and early post-operative complication and lymphocyst formation rates were 2.0%(bowel complication 0.7%; urinary tract complications 0.5%; nerve injuries 0.5%), 2.9% and 7.1%, respectively.

7.1 RCTs comparing laparotomy to minimally invasive surgery for endometrial cancer

In the LAP-2 study, an RCT carried out by the Gynecologic Oncology Group (GOG), 2,616 patients with endometrial carcinoma confined to the uterus were randomly assigned to laparoscopy or laparotomy (Walker, 2009). All patients had complete surgical staging including PLND and PaLND. Laparoscopic-assisted vaginal hysterectomy, total laparoscopic hysterectomy or robotic-assisted total laparoscopic hysterectomy was allowed. They found that laparoscopy resulted in similar intra-operative complications, fewer post-operative moderate or severe adverse events (14% versus 21% by laparotomy, $p<0.0001$), shorter hospital stay, less use of pain medication and quicker resumption of daily activities but required longer operating time. Twenty five percent of patients randomized to laparoscopy were converted to laparotomy. Patients at higher risk for a conversion to laparotomy were elderly (>63 years) and those with metastatic disease and a high BMI (17% in patients with a BMI of 25kg/m^2, 26% with a BMI of 35kg/m^2, 57% with a BMI >40kg/m^2).

In an Australian RCT (n=361), which also compared total laparoscopic hysterectomy with abdominal hysterectomy in early endometrial carcinoma, 52% of the patients had a pelvic or para-aortic lymphadenectomy. Only 2.4% of patients assigned to laparoscopy were converted to laparotomy. Patients who had laparoscopic surgery reported significantly greater improvement in QoL from baseline compared with those who had laparotomy, this difference persisted for up to 6 months after surgery. Operating time was significantly longer in the laparoscopy group (138 minutes [SD 43]) versus 109 minutes [SD 34]; p=0.001). Intra-operative adverse events were similar between groups (laparotomy 5.6% versus laparoscopy 7.4%]; p=0.53), but postoperatively, twice as many patients in the laparotomy group experienced adverse events of Grade 3 or higher (23.2% versus 11.6%; p=0.004). The authors concluded that QoL improvements from baseline during early and later phases of recovery, and the adverse event profile, favor laparoscopy over laparotomy for the treatment of Stage I endometrial cancer.

Other studies that investigated the feasibility of minimally invasive surgery (laparoscopy and robot-assisted surgery) in elderly and obese patients concluded that neither age nor BMI is a contraindication to minimally invasive procedures, as it is these patients who benefit the most (Boggess et al., 2008; Gehrig et al., 2008; Janda et al., 2010; Obermair et al., 2005; Scribner et al., 2001).

8. Radiotherapy (RT)

Can adjuvant radiotherapy increase disease-free and/or overall survival after standard surgery? In other words, can radiotherapy make up for incomplete staging if the characteristics of the cancer at final pathology appear to be worse? Several studies have addressed this question.

8.1 Studies

The Postoperative Radiation Therapy in Endometrial Cancer (PORTEC) Trial randomized 715 patients with Stage IB (Grades 2 and 3) and with IC (Grades 1 and 2) endometrial cancer after standard surgery without PLND to observation or pelvic RT with 46 Gy. Although the five-year actuarial locoregional recurrence rates were 4% in the radiotherapy group and 14% in the control group (p=0.001, the overall survival rates were similar in the two groups: 81% (radiotherapy) and 85% (controls), p=0.31. Endometrial-cancer-related death rates were 9% in the radiotherapy group and 6% in the control group (p=0.37). Treatment-related complications occurred in 25% of radiotherapy patients and in 6% of the controls (p=0.0001). One third of the complications were Grade 2 or higher. Seven out of eight Grade 3 to 4 complications were in the radiotherapy group (2%). The observation that the higher incidence of locoregional recurrences in the control group is not reflected in the overall survival was explained by the post-relapse survival. Twenty-three out of 51 patients with a locoregional relapse died, of whom only seven died due to their locoregional recurrence. By contrast, 21 of 30 patients with distant metastases as first failure died, of whom 19 died from the metastases. Salvage treatment of vaginal relapse was often successful. After vaginal recurrence, the two-year survival rate was 79% in contrast to 21% after pelvic or distant relapse. At three years, the survival was 69% and 13%, respectively (p=0.001). As for the survival after first relapse by treatment arm, the survival rate was better for patients in the control group than for patients in the radiotherapy group (p=0.02). The authors concluded that post-operative radiotherapy in Stage 1 endometrial carcinoma reduces locoregional recurrence but has no impact on overall survival and that radiotherapy increases treatment-related morbidity. Therefore, a trade-off between the risk of locoregional recurrence and the survival rate after salvage treatment on the one hand, and the morbidity and cost of adjuvant pelvic radiotherapy on the other, has to be made for each subgroup of Stage 1 endometrial carcinoma. These findings further support the need for a systematic LND whenever possible for patients with intermediate or high risk of endometrial cancer.

8.2 Conclusion

Adjuvant radiotherapy cannot be substituted for a systematic LND in intermediate- and high-risk endometrial cancer patients.

9. Areas for future research

9.1 Sentinel Lymph Node (SLN)

From the evidence presented above, it is clear that for patients with endometrial cancer who are at risk of lymph node metastasis, the site of metastasis can be in the pelvic LNs or the para-aortic LN chain up to the renal vessels. Removal of metastatic lymph nodes has prognostic and therapeutic value. On the other hand, the addition of a systematic PLND and PaLND to a standard hysterectomy and bilateral salpingo-oophorectomy, increases the

technical difficulty of the surgery, requires more operating time and increases the risk of intra-operative and postoperative complications. These problems apply even when a minimally invasive surgical approach is adopted. Therefore, the challenge is to identify a surgical technique that provides accurate staging information about nodal status, while avoiding unnecessary morbidity.

Sentinel lymph node detection might resolve this dilemma. This technique is based upon the observation that in several types of cancer, tumor cells migrate from the primary tumor to one or a few lymph nodes before metastasizing to other lymph nodes (melanoma, breast, cervix, vulva) (Altgassen et al., 2008; Hauspy et al., 2007a&b). Lymphatic mapping by sentinel lymph node (SLN) detection offers a means of assessing the lymph node status of primary tumors with respect to metastases, without having to resort to formal LND.

In a meta-analysis of various techniques to assess lymph node status in endometrial cancer, Selmanet al. (2008) showed that SLN biopsy was more accurate than MRI and CT scan. In endometrial cancer, several approaches have been attempted: serosal injection during surgery, cervical injection or peri-tumoral injection using hysteroscopic assistance. With cervical injection, detection rates of sentinel lymph nodes in low-risk endometrial cancer reach 85% (Abu-Rustum et al., 2009). A recent study in early invasive cancer suggested that SLN biopsy is a more sensitive procedure to detect pelvic lymph node metastasis compared to the classic PLND due to more extensive sectioning by the pathologist of this LN, its occasionally unusual location (common iliac or para-aortic) and the surgeon's thorough search for this blue or "hot" node (Gortzak-Uzan et al., 2010). Similarly, in early-stage endometrial cancer, SLN mapping appears to be a more sensitive procedure for detecting PLN metastasis compared to the classic PLND for the same reasons: the surgeon's thorough search for this sentinel node and extensive sectioning by the pathologist of the sentinel lymph node (Khoury-Collado et al., 2011).

A French multicentre study (SENTI-ENDO) prospectively evaluated the ability of cervical dual injection of technetium and patent blue to identify SLN in patients with endometrial cancer (Ballester et al 2011). One hundred thirty-three patients were enrolled at nine centers in France. At least one SLN was detected in 111 of the 125 eligible patients; 17% had pelvic lymph node metastases and 5% had an associated SLN in the para-aortic area. Three patients had false-negative results (two had metastatic nodes in the contralateral pelvic area and one in the para-aortic area), giving an NPV of 97% (95% CI 91 to 99) and sensitivity of 84% (62 to 95). All three of the patients in whom the SLN was negative in the presence of metastatic nodes had Type 2 endometrial cancer. Ultrastaging detected metastases, which were missed by conventional histology in nine of 111 (8%) patients with detected SLNs, representing nine of the 19 patients (47%) with metastases. SLN biopsy upstaged 10% of patients with low-risk and 15% of those with intermediate-risk endometrial cancer.

This study highlights the danger of omitting lymphadenectomy in patients with early-stage endometrial cancer, as suggested by the ASTEC study, as 11% of patients at low risk for lymph node metastasis (Grade 1, endometrioid cancer with no myometrial invasion), had positive lymph node metastasis. The authors conclude that SLN biopsy with cervical dual labeling could be a trade-off between systematic LND and no dissection at all in patients with low or intermediate risk endometrial cancer.

The limitations with this study are that the investigators used only cervical injection for the SLN mapping, which is not ideal to identify PaLNs. In a review of SLNs in endometrial cancer, Delpech et al 2008, reported a lower rate of para-aortic SLN detection using cervical

injection alone compared with cervical and subserosal or subendometrial injection of patent blue. Additionally, in the SENTI-ENDO study, PaLND was not done if the PLND did not identify metastasis. This means that the incidence of para-aortic metastases could have been underestimated, as about 10% to 16% of lymph node metastases occur exclusively in the para-aortic region.

An experimental study on female cadavers by Lecuru et al 1997, had identified that one of the main routes of lymphatic drainage from the uterus ran along the infundibulo-pelvic ligament to the para-aortic area. Furthermore, when sentinel lymph node were identified using hysteroscopic injection to the tumor base, the para-aortic region was shown to be an important site of sentinel nodes in endometrial cancer, with 14% of SLN being exclusively in the para-aortic region and 47% of para-aortic sentinel nodes located above the inferior mesenteric artery (Nijkura et al., 2004). This method is technically more demanding. Nevertheless, if sentinel lymph node mapping is to replace surgical staging for endometrial cancer, we are obliged to investigate and adopt the most accurate rather than the most expedient method of identifying the sentinel lymph node.

10. Conclusion

Patients who have Grade I/II, endometrioid adenocarinoma with minimal myometrial invasion have very low risk of lymph node metastasis and do not benefit from LND. However, only a thoroughly detailed intra-operative frozen section can identify this subgroup. All high-risk patients need a systematic PLND as well as a PaLND up to the renal vessels. Such dissection needs considerable technical skills on the part of surgeons, and has risk for patients; but confers a significant survival advantage. Analysis of numerous nodes, particularly when they are small, is tedious for the pathologist. Therefore, SLN mapping has the potential to identify the subset of low-/intermediate-risk patients who do not need lymph node dissection. Research needs to be directed at finding the most accurate method of identifying the sentinel lymph node/nodes in endometrial cancer. This will allow the judicious use of resources, including time, cost and energy, to recover the appropriate number of lymph nodes in high-risk patients who will benefit from this procedure.

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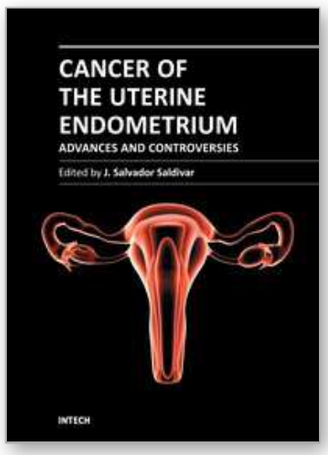

Cancer of the Uterine Endometrium - Advances and Controversies
Edited by Dr J.S. Saldivar

ISBN 978-953-51-0142-0
Hard cover, 182 pages
Publisher InTech
Published online 29, February, 2012
Published in print edition February, 2012

The book Cancer of the Uterine Endometrium - Advances and Controversies brings together an international collaboration of authors who share their contributions for the management of endometrial carcinoma. The scope of the text is not basic, but rather aims to provide a comprehensive and updated source of advances in the diagnosis and therapeutic strategies in this field of gynecologic cancer. Each section in the book attempts to provide the most relevant evidence-based information in the biology and genetics, modern imaging, surgery and staging, and therapies for endometrial cancer. It is hoped that future editions will bring additional authors to contribute to this endeavor. To this end, it is our patients who will benefit from this work.

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