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9. The role of cytoreductive surgery in cervical cancer: Is there a benefit of retroperitoneal lymph node debulking in advanced disease?

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Abstract. Cervical carcinoma commonly spreads via the lymphatics, with metastases first occurring in the pelvic lymph nodes, and then sequentially spreading to the paraaortic nodes. Data from retrospective studies suggest that there may be a survival benefit in those patients with macroscopic nodal disease which is debulked to microscopic residual. In patients undergoing chemo-radiation, isolated failure in the lymph nodes is uncommon and is more commonly associated with failure to control the primary tumor. Candidates for surgical debulking of lymph nodes should be selected among patients with a high probability of achieving local control, a low likelihood of developing distant metastases, and lymph nodes of sufficient size that control with chemo-radiation is unlikely.

Introduction

Cervical cancer remains the only gynecologic cancer, which is clinically staged by FIGO. This implies that the treatment is frequently driven by characteristics of the primary tumor without accurate knowledge of the tumor extent. As in other gynaecologic malignancies, non invasive diagnostic tests

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have not been shown to be accurate in identifying metastatic disease, [1] leaving surgery as the only reliable method of determining exact information regarding local tumor spread, lymph node metastases, and involvement of adjacent organs. Despite this, the value and benefit of surgical staging remain controversial.

To date, there are no randomized data supporting a survival advantage for surgical staging or debulking of lymph nodes; though retrospective data suggests a potential benefit for lymph node debulking in women with bulky metastatic disease [2-7].

Cervical carcinoma commonly spreads via the lymphatics, with metastases first occurring in the pelvic lymph nodes and then sequentially spreading to the paraaortic nodes [8]. The frequency of pelvic and aortic node metastases increases with the stage of disease (table 1).

The sensitivity of various tests in identifying patients with positive lymph nodes is low; 55% for MRI and CT, and 75% for PET [1]. Though most of the false negatives correspond to microscopic disease or a slightly enlarged lymph node measuring less that 2 cm (which is associated with a high degree of success if included in the success field) [10].

Currently the main value of diagnostic imaging in advanced disease is the detection of metastatic lymph nodes outside the pelvis. If debulking of enlarged lymph nodes is performed, then determination of the size and location of the enlarged lymph nodes, and the characteristics of the primary tumor will help identify appropriate surgical candidates for lymph node debulking.

Table 1. Frequency on Pelvic and Aortic Node Metastases Detected with Pretreatment Staging Laparotomy (Data from Morrow et al) [9].

Clinical Stage	Total Cases	Aortic Metastases (%)	Pelvic Metastases (%)
Ib	570	6	-
IIa	174	12	-
IIb	421	21	24
III, IVa	615	31	50

Evidence supporting lymph node debulking in locally advance cervical cancer

Six retrospective studies have reported on outcomes after surgical lymph node debulking (table 2) [2-7]. Five of the six studies debulked both pelvic and paraaortic lymph nodes, and the sixth study debulked paraaortic lymph nodes only.

Table 2. Survival data from studies assessing lymph node debulking.

Author	N	Nodal Sites	Surv (-) Node	Surv Mic Nodes	Surv Macr Debulked	Surv Macr Unresect
Morice [6]	421	PLN, PA	94%	75%	40%	—
Hacker[4]	34	PLN, PA	N/A	80%	82–90%	N/A
Downey [3]	156	PLN, PA	85%	57%	51%	0%
Potish [7]	159	PLN, PA	86%	56%	57%	0%
Cosin[2]	266	PLN, PA	75%	43%	50%	0%
Kim[5]	43	PA	N/A	*18 months	24 months	—

*(median survival)

Survival information is provided on patients with negative lymph nodes, microscopically involved nodes, and macroscopically involved nodes in whom the nodes were surgically debulked. Each of the 6 studies demonstrated similar survivals between patients with microscopically involved nodes and patients with macroscopically involved that were successfully debulked. No long term survivors were reported in patients with unresected macroscopic lymph nodes. Unfortunately, the definition of macroscopic nodal disease was stated in only two of the studies ($\geq$1.5 cm) [4, 6].

The inference from these reports is that there may be a survival benefit in patients with macroscopic nodal disease which is debulked to "microscopic residual." The 5-year survival rates in patients with macroscopically debulked pelvic lymph nodes, stage IB–IVB, ranged from 46 to 90%, and 50-80% for patients with microscopic nodal disease.

Despite these encouraging results, strict selection is required. Patients in whom there is a low likelihood of obtaining pelvic control or have a high probability of harbouring unrecognized distant metastases are not likely to benefit from lymph node debulking. Importantly, patients with mildly enlarged lymph nodes (less than 2 cm) that are likely to be successfully treated with chemo-radiation, will have minimal impact from surgical debulking of lymph nodes on their survival. These different patient populations will be addressed in the following paragraphs.

Identifying the ideal candidate

The typical dose that is delivered to the pelvic lymph nodes with acceptable morbidity using external beam radiation is 6000 cGy. This dose

will control 90% of lesions up to 2 cm in size. However, radiation therapy's efficacy declines as involved nodal size increases [10] and therefore there is a potential role for surgery. The addition of chemotherapy to radiation has been shown to further decrease local failure by 33–50% [11-14].

As a prerequisite for retroperitoneal lymph node debulking to have a therapeutic benefit, chemo-radiation should have a high chance of sterilizing the primary tumor, and there should be a low risk of unrecognized distant metastatic disease. In this scenario, removing bulky metastatic pelvic nodes should increase pelvic control above that from chemo-radiation alone by improving side wall control as well as theoretcially decreasing extra pelvic failures or distant failures.

Likelihood of achieving tumor control

Failure in achieving local control with radiation is a key prognostic factor in advanced stage cervical cancer. Patients with grossly positive hysterectomy specimens after radiation, progress and died at almost 7 times the rate compared to those with negative specimens [15]. Additionally, the incidence of distant metastases is 40 to 60% greater in patients in whom pelvic control is not attained [16] (Table 3).

Tumor size is the most important predictor of pelvic control. In one GOG report evaluating stages IIB–IVA patients treated with radiation and other agents on three GOG trials [17], patients had progressively worsening prognosis with increasing tumor size.

In an attempt to categorize patients by tumour size, 8 cm has been identified as a clinically relevant cutoff. Patients with tumor sizes larger than 8 cm have been associated with worse survival [18] and central tumor control rates [19] when compared with those smaller than 8 cm.

Other tumour factors (table 4), that correlate inversely with achieving tumor control include bilateral pelvic sidewall involvement, hydronephrosis, and lower vaginal involvement [20].

Table 3. Association of pelvic failure and developing distant metastases by different FIGO stages [16].

FIGO Stage	**Distant Metastases**	
	Local control (%)	**Pelvic failure (%)**
IB	11	76
IIA	22	88
IIB	21	62
III	34	87
IVA	50	75

Table 4. Local tumor factors associated with survival in stage IIIB cervical cancer [20].

Tumor Size (IIIB)	**5y-DSS**
<6	59
6-7.9	48
≥8	30
Extent of Tumor (IIIB)	**5y-DSS**
No pelvic wall	34
Fixed to one side	44
Fixed both sides	27
Hydronephrosis (IIIB)	**5y-DSS**
Absent	40
Present	28
Vagina Lower 1/3	**5y-DSS**
Not involved	38
Involved	25

5y-DSS: 5 years disease specific survival

Patients with high likelihood of distant spread

There are 2 patient populations at high risk for development of distant disease; patients with large tumor volume who are unlikely to achieve pelvic control, and women with positive nodes. The location of lymph node metastases along the lymphatic chain correlates with the site of recurrence and survival. Location of enlarged nodes correlates with the likelihood of developing systemic disease and mortality.

Patients with common iliac and paraaortic lymph node metastases have the highest rates of distant spread; up to 60% [21]. Based on the above data, the value of lymph node debulking would be appear to be unjustified in these patients with high level nodal disease due to their significant risk of distant spread.

Residual disease after chemo-radiation. Are all good prognosis patients appropriate candidates for surgery?

In order for lymph node debulking to have a therapeutic role, it should be able to salvage patients whose primary tumor is controlled after radiation, but residual or persistent metastatic disease remains in their lymph nodes.

We hypothesized in 2002, through mathematical modeling that the benefit of performing a retroperitoneal lymph node dissection in all patients with locally advanced cervical cancer was unjustified given that it benefited only a small proportion of patients [22]. This has been confirmed with data presenting residual disease in the uterus and lymph nodes after treatment with chemo-radiation [23-27] (table 5).

There are several studies evaluating the role of surgery after radiation (and chemo-radiation) that provide important information about persistent disease in the cervix and lymph nodes [23-27] . In these studies the most common site for persistent disease is the primary tumor. Among the group of patients that have persistent disease in the lymph nodes, the majority also have persistent central disease, leaving only a small number of patients with isolated persistent nodal disease. Thus, if one performs a lymphadenectomy on every patient prior to radiation, theoretically only those destined to persist with isolated nodal persistent disease will benefit, which corresponds to approximately 0 to 6 % of all patients.

In the only study where patients with pre-irradiation enlarged lymph nodes were included, there were just 4 among 113 patients with isolated persistent disease in the lymph nodes [25].

Table 5. Residual disease in patients with locally advance cervical cancer treated with surgery after radiation or chemoradiation.

	N	(+) Primary (N)	(+) PLND (N)	(+) Primary & PLND (N)	(+) PLND alone (N)
Huguet 2008 [26]	92	45.6% (42)	6.5% (6)	6.5% (6)	0
Ferrandina 2007 [24]	152	NA	12.5% (19)	9.2% (14)	2.6% (4)
Houvenaeghel 2006[25]	113	51% (57)	15.9% (18)	11.5% (13)	3.5% (4)
Rouzier 2005 [27]	360	49.4% (178)	27.5% (99)	21.4% (77)	6.1% (22)
Classe 2006 [23]	175	61.1% (107)	24% (42)	23.4% (41)	0.6% (1)

PLND: Pelvic lymph nodes

Surgical approaches, feasibility and complications

There are four basic approaches to debulking retroperitoneal nodes in cervical cancer patients: extraperitoneal laparotomy, transperitoneal laparotomy, extraperitoneal laparoscopy and transperitoneal laparoscopy. Data from a

randomized control trial comparing the extraperitoneal to the transperitoneal approach by laparotomy in paraaortic staging of patients with locally advanced cervical cancer reveal both techniques are of similar sensitivity in detecting nodal spread. There is no significant difference in the frequency of surgical complications. Although the proportion of patients receiving an acceptable dosage of radiation therapy was similar, the transperitoneal approach was associated with a higher frequency of post irradiation enteric complications (11.5% vs 3.9%) [28].

No data regarding delays in starting radiation therapy was provided, however the data suggests that the extraperitoneal approach by laparotomy may be preferred when surgical lymph node debulking is performed.

Over the past 10 years, laparoscopy has been used as an alternative to laparotomy for staging of cervical cancer. An Italian randomized control trial in 168 women with stage IB–IIB cervical carcinoma scheduled for radical hysterectomy and randomized to transperitoneal, extraperitoneal or laparoscopic pelvic lymphadenectomy showed that extraperitoneal and transperitoneal open lymphadenectomy were as feasible and effective as the laparoscopic approach (96%, 93% and 95% respectively) with similar acceptable complication rate [29]. Operative time was longer and length of hospital stay was shorter in the laparoscopic group.

Observational studies addressing staging in advanced stage cervical cancer have shown that the laparoscopic approach is associated with acceptable morbidity and similar success rates compared with laparotomy. However, there were not enough patients with bulky enlarged nodes to make conclusions regarding debulking enlarged lymph nodes. In a large series of 98 patients with locally advanced cervical cancer, only half of the patients with positive nodes could be resected (19 out of 38 cases) [30]. Querleu in his series of 51 patients, found that only 6 of 9 patients with macroscopically involved lymph nodes could be debulked laparoscopically [31].

In summary, for staging purposes all approaches have shown similar efficacy, but the retroperitoneal approach and the laparoscopic approach have the advantage of less enteric complications from radiation therapy. For debulking purposes there is no comparative data among these techniques and data from observational studies suggest that a laparotomy may be more appropriate.

All series demonstrate that retroperitoneal lymph node dissections can be completed in most patients with locally advanced cervical cancer, with a feasibility ranging from 92 to 100 % (table 6) [2-7]. However, in these series the majority of patients had either normal or microscopically involved lymph nodes.

When analyzing patients with macroscopically involved nodes, feasibility decreases. In a recent publication with 78 patients with enlarged nodes, 16 were considered unresectable during surgery. In this study the

Table 6. Feasibility and Complication of Lymphadenectomy in Patients with Locally advance Cervical Cancer.

Author	N	Nodal Sites	Succesful procedure	Complications
Morice[6]	421	PLN, PA	100%	lymphocysts 6.2%, urinary tract fistulae 2.8%, bowel obst 0.5%
Hacker[4]	34	PLN, PA	100%	14.7% (5)1 vascular, 2 infect lymphocyst, 1 fascitis, 1 hepatitis
Downey[3]	156	PLN, PA	94.2%	
Cosin[2]	266	PLN, PA	92.5%	6.7% (18) drain of lymphocyst
Marnitz[32]	84 lpx	PLN, PA		8 drain of lymphocele
Querleu[31]	53 lpx	PA	96%	1 ureter. 1 hematoma. 2 lymphocyst (req drain). 1 unrelated Bowel obstr
LeBlanc[33]	181 lpx	PA	95%	3
Zighelboim[34]	104	PLN,PA	85%	6 vascular (repaired intraop) lymphocyst 2%, wound complic 8%
Denschlag[35]	59 extraperitoneal open	PLND & PA if + pelvic	100%	lymphocyst 12% (7), wound infect 3%(2), v cava injury 1%(1), blader inj 1%(1)

chance of achieving a successful resection decreased with increasing age and size of largest lymph node. For the 16 patients who had incomplete resections, the median intraoperative size of the largest lymph node was 4.0 cm. The reason given by the operating surgeons for their inability to completely remove the lymph nodes were vascular involvement of the lymph node (37.5%), infiltration into the bone (19%), neural invasion (12.5%) and gross nodal involvement above the superior mesenteric artery (6%) [34].

Surgical staging of women with locally advanced cervical cancer can be performed with acceptable morbidity. The most common complication is lymphocyst; occurring in approximately 10% of cases (particularly when an extraperitoneal lymphadectomy is performed). It is lower for retroperitoneal laparoscopic staging when the peritoneum is perforated (5% incidence) [31].

Other complications reported include vascular, ureteric, and bladder injuries (0-6%).

There does not appear to be a significant delay in starting radiotherapy after a lymph node dissection. The median time interval between surgery and the start of chemo-radiation using laparoscopy is approximately 10 days [32], and less than 3 weeks for extraperitoneal laparotomy [2, 35, 36].

Conclusion

Data analyzed from surgical specimens of the uterus and lymph nodes after chemo-radiation supports the premise that retroperitoneal lymph node dissection in locally advanced cervical cancer is not likely to benefit many patients, as the most common site for persistent disease is the primary tumor. Isolated nodal disease after chemo-radiation presents in only 0 to 6 % of the patients.

Data from debulking lymph nodes prior to radiation suggest that there may be a small number of patients that benefit. In general, these patients have a high likelihood of control of central disease, a high chance of successfully debulking the macroscopically enlarged lymph nodes, and a low probability of distant metastatic disease.

Patients with tumor sizes larger than 8 cm, bilateral pelvic sidewall involvement, hydronephrosis, and lower vaginal involvement [20] have been associated with a worse survival [18] and central tumor control rates [19], and are poor candidates for retroperitoneal debulking.

Additionally, patients at high risk of distant disease should be excluded from lymph node debulking. Distant metastatic disease has been correlated with both primary tumor characteristics and with the site and volume of lymph node disease. Site of lymph node disease correlates with site of recurrence and survival. Patients with paraaortic and common iliac lymph node disease develop distant disease in up to 60% of cases [21, 37, 38].

Thirdly, the likelihood of successfully debulking the macroscopically enlarged lymph nodes should be high. Nodes that on imaging are suspicious for vascular, neural and bone invasion, as well as those larger than 5 cm should be excluded. Unfortunately, preoperative tests are not very accurate in identifying invasion to these structures and it remains for the most part an intra-operative diagnosis.

The ideal candidates for considering lymph node debulking have the following characteristics: Stage IB or IIB, tumour >2 cm and <8 cm, stage IIIB with unilateral disease only, macroscopically enlarged lymph nodes confined to the pelvis (>2 cm and <5 cm), and normal size common iliac and paraaortic nodes.

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