Distinguished Expert Series

Patients with locally advanced cervical cancer should not undergo routine pretreatment surgical staging

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Summary

The current FIGO staging system for locally advanced cervical cancer (Stages IIB to IVA) is considerably inaccurate, especially because lymph node metastases are ignored. Surgical staging has been used to overcome this insufficiency, allowing individualisation of therapy. However, this approach is controversial and should not be routinely undertaken considering the feasibility, adequacy and morbidity involved with the surgical procedure. Moreover, the survival benefit of surgical staging has yet to be proven and accurate non-invasive imaging alternatives, such as position emission tomography (PET) scanning, have become available.

The management of patients with locally advanced cervical cancer based on PET and computed tomography (CT) imaging is proposed and discussed.

Key words: Locally advanced cervical cancer; Surgical staging; Clinical staging, PET scanning.

Introduction

Unlike ovarian and endometrial cancers which are at present surgically staged, cervical cancer remains a clinically staged tumour. The justification for this comes from the fact that most patients will be treated by radiotherapy, and because there is a lack of uniformly available technology worldwide to evaluate the extent of the disease. The staging procedure should be done as uniformly as possible not only as a means of evaluating treatment strategies within one institution, but also to compare results from different institutions throughout the world. Only if the rules for staging are strictly observed is it possible to compare results using different modalities of treatment. It should be remembered, though, that cervical cancer staging does not limit treatment strategies which must be tailored to the disease on an individual basis.

However, the current FIGO (International Federation of Gynaecology and Obstetrics) staging system for cervical cancer, especially for locally advanced disease (Stages IIB to IVA) is unreliable because, among other factors, the most relevant predictor of survival, i.e. lymph node metastasis, is ignored. Furthermore, other variables like intraperitoneal disease are also not taken into account for staging the tumour. A discordance has been documented of around 50% between clinical and the subsequent surgical staging [1-3]. Operative findings are reported to show more advanced stages of disease than suspected in up to 40% of cases. In addition, up to 14% of patients may be overstaged because a benign condition is discovered during surgery, such as pelvic inflammatory disease, endometriosis, or both, that may lead to the clinical impression of parametrial involvement. This prompted several investigators, in the early 1970s, to perform pre-treatment surgical staging in locally advanced cervical cancer patients, in order to accurately define the extent of the disease, which is critical for treatment planning and has paramount prognostic significance. Several reports have shown that in up to 40% of the patients surgically staged the radiation fields had to be extended in order to encompass extrapelvic disease lying outside the conventional fields [4, 5], thereby allowing individualisation of therapy. Treatment with extended volume radiation fields can result in salvaging some of these patients [6], especially if concurrent chemotherapy is used, even in patients with metastatic paraaortic nodes [7]. However, the surgical method that was used, at that time, to evaluate the dissemination of the tumour consisted of a transperitoneal laparotomy with peritoneal washings, exploration of the entire abdominal cavity with biopsy or excision of any suspicious lesion and a complete pelvic and paraaortic lymphadenectomy. This surgical approach, generally followed by radiotherapy, was responsible for high and unacceptable morbidity and even mortality rates. Morbidity was not only related to the surgical procedure, but was mainly radiation-related, and consisted predominantly of gastrointestinal and genitourinary complications [8].

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Surgical Staging

Considering that the clinical staging of patients with cervical cancer is unable to evaluate the lymph node status, and this evaluation is considerably inaccurate using lymphangiography (restricted to few centres with the expertise), computed tomography (CT) and magnetic resonance imaging (MRI) – both with sensitivities varying between 35% and 68% for detecting pelvic and paraaortic metastases [4, 9] – and finally, because surgical staging remains the gold standard for the detection of occult nodal disease, researchers started, in the 1980s, to perform extraperitoneal laparotomy, reducing complication rates [3, 10]. Later, the introduction of extraperitoneal laparoscopy shortened the hospital stay, further reduced the complication rates associated with less long-term radiation morbidity – probably because of reduced postoperative intraabdominal adhesions – and thus, became the standard pretreatment surgical staging in patients with locally advanced cervical cancer. Nevertheless, pretreatment surgical staging in this population is controversial and, in our opinion, should not be routinely carried out. The reasons for this come from the feasibility, adequacy and morbidity related to the surgical procedure. Furthermore, the survival benefit of surgical staging has yet to be proven and, notably, novel and accurate non-invasive imaging alternatives to surgery have recently become available. Every one of these issues is going to be discussed.

Why surgical staging should not be routinely used

In terms of the **feasibility** of surgical staging in locally advanced cervical cancer, it is important to remember that not many centres have laparoscopic expertise, the procedure relies on technical support not easily available, there is also a shortage of training programmes, surgical staging is not practical or even possible in many patients (e.g., morbid obesity and abdominal adhesions, to cite only a few) and, finally, there are contraindications to surgery in some patients.

The **adequacy of lymphadenectomy** is problematic. Even in experienced hands, especially paraaortic lymphadenectomy is incomplete in a number of patients, and the nodes are frequently unresectable. Table 1 shows the results of a survey of recent literature where incomplete lymphadenectomy was documented to occur 9% of the time, and 19% of the lymph nodes were unresectable due to the intimate adherence of the enlarged and infiltrated nodes to the adjacent blood vessels.

Table 1. — *Laparoscopic staging in cervical cancer. Adequacy of lymphadenectomy.*

Study (ref.)	n	unresectable nodes (%)	incomplete lymphadenectomy (%)
Vidaurreta *et al.*, 1999 [30]	91	21	8
Querleu *et al.*, 2000 [31]	51	6	12
Schlaerth *et al.* (GOG), 2002 [32]	67	25	9
Total	209	19	9

Table 2. — *Complications of laparoscopic extraperitoneal paraaortic lymphadenectomy.*

Study (ref.)	n	IOC + POC		
		Minor (%)	Major (%)	Conversion laparotomy (%)
Querleu *et al.*, 2000 [31]	51	2	8	0
Vergote *et al.*, 2002 [33]	21	0	5	0
Sonoda *et al.*, 2003 [34]	111	11	2	0
Mehra *et al.*, 2004 [35]	32	19	6	3
Total	215	9	4	0.5

IOC = intraoperative complications. POC = postoperative complications.

Although mortality is an extremely rare event associated with the new laparoscopic techniques, **morbidity** remains a common concern with diverse facets. The intrinsic morbidity directly related to the surgical procedure, such as: the rare documented cases of peritoneal tumour dissemination [11], the few trocar-site metastases [12, 13] and, although, conversion to laparotomy is infrequent (mainly due to abdominal adhesions, vascular injury or equipment failure) there are a number of both minor and major complications either intra- or postoperative, as depicted in Table 2. This table presents recent data on the complication rates of laparoscopic extraperitoneal paraaortic lymphadenectomy. Minor complications, both intra- and postoperative, occurred in 9% of patients (predominantly lymphoceles, some of which had to be surgically drained), whereas major complications were recorded in 4% of the cases, such as, vascular injury, ureter transection, bowel obstruction and pulmonary embolism. As outlined previously, with the use of the extraperitoneal approach for surgical staging and its combination with the laparoscopic route, there was a significant decrease in the radiation-related morbidity after surgery. Nevertheless, major gastrointestinal and genitourinary complications as high as 4% have been documented by Weiser and co-workers in a GOG (Gynecologic Oncology Group) study after extraperitoneal lymphadenectomy [10]. Moreover, radiation-related morbidity, even after extraperitoneal laparoscopy, should not be disregarded especially when concurrent chemotherapy is used with extended field radiotherapy.

One should try to answer the following question: although surgical staging definitely improves identification of nodal disease, allows individualisation of therapy (extending the radiation fields), and has prognostic relevance, does it contribute to the quality of life and, particularly, does it give a **survival benefit** to the patient?

Some retrospective studies have shown a survival advantage for those patients whose enlarged metastatic lymph nodes had been successfully debulked [14, 15]. However, even the theoretical survival benefit of surgical staging is minimal. It is known that in locally advanced cervical cancer (Stages IIB to IVA) positive paraaortic nodes are identified in approximately 24% of the patients, as Heller in a GOG study [16] and others have documented. Considering that extended field radiotherapy can salvage 25% to 30% of patients with paraaortic nodal disease [7, 17], only about 6% of patients with advanced cervical cancer undergoing a staging laparotomy/laparoscopy with node debulking would have a survival benefit as a consequence of the altered therapy. Other investigators even challenge this small theoretical benefit arguing that patients with metastatic paraaortic nodes often have undiagnosed occult distant metastases in up to 60% of cases [18]. Consequently, such patients should be offered more effective systemic therapy than the one currently available to control their disease.

The only prospective randomised controlled study published to date, by Lai and colleagues in 2003 [19], comparing clinical with surgical staging in locally advanced cervical carcinomas, demonstrated a detrimental effect on both progression-free and overall survival for the surgical arm. Although this study may be criticised due to the small number of patients recruited (29 submitted to clinical staging and 32 undergoing surgical staging), accrual of patients was terminated according to early stopping rules when an interim analysis showed a significantly worse outcome in terms of progression-free survival ($p = 0.003$) and overall survival ($p = 0.024$) for patients in the surgical arm.

The researchers pointed out that there was a delay in starting radiotherapy in the surgical staging group. Furthermore, one can speculate that the detrimental effects of surgical staging on survival could be explained by the impairment of both humoral and cellular immune responses after surgery which is particularly deleterious in cancer patients [20]. The risk of tumour recurrence is also increased if this immune suppression is not reversed after definitive treatment, according to Cole and Humphrey [21]. Consideration should also be paid to the decreased postoperative radiation effectiveness due to tumour bed hypoxia and accelerated repopulation of any surviving clonogenic cells. In addition, tumour hypoxia has also been linked to induction of angiogenesis and increased metastatic potential of the tumour.

Another strong argument to avoid surgical staging in locally advanced cervical cancer derives from the fact that recently non-invasive alternatives have become available. **FDG-PET scanning** (fluoro-deoxy-glucose positron emission tomography) has been shown to be a superior imaging technique to assess lymph node metastases; superior to sonography, CT, MRI and lymphangiography. In contrast to these techniques which rely on morphology, above all size criteria (node diameter ≥ 1 cm), PET scanning is a functional imaging modality that can assess the metabolic activity of malignant cells. The accuracy of PET to detect pelvic nodal disease is higher than 90% (Table 3). Among 70 patients with cervical cancer who had normal pelvic nodes by CT scan or MRI and underwent PET scanning before surgical staging lymphadenectomy, PET had a sensitivity of 91% and a specificity of 98% for detection of pelvic nodal disease (Table 3). Moreover, PET scanning had a sensitivity of 82% and a specificity of 95% for predicting disease in the paraaortic lymph nodes, as a survey of the literature, also restricted to surgicopathologic studies, has shown (Table 4). The few false-positive results associated with PET imaging come from inflammatory areas within the nodes. The approximate 20% of false negatives missed by PET corresponded to microscopic nodal metastases. Since PET scanning can also accurately identify the primary cervical tumour and its extension, PET is being used as an adjunct to clinical staging in several centres to optimise treatment planning. In this setting, a few recently published reports have already documented that PET represents a non-invasive alternative to surgical staging. Grigsby and co-workers [22] demonstrated the clinical utility of PET scanning, showing that the progression-free survival in advanced cervical cancer patients correlates to findings from PET/CT imaging. The survival rate after radiotherapy with concomitant chemotherapy was significantly higher in PET/CT negative paraaortic nodal disease in comparison to patients with PET positive nodes. Survival remained significantly higher ($p < 0.0001$) in the PET negative group in comparison to the subset of patients with small volume paraaortic metastases (PET positive but CT negative imaging). This study confirms the prognostic importance of paraaortic nodal disease, and also demonstrates that patients even with small volume metastasis to the paraaortic nodes have a dismal prognosis with the currently available therapeutic regimens.

Table 3. — *PET scan detection of pelvic nodal metastasis in cervical cancer. Surgicopathologic studies.*

Study (ref.)	n	Sensitivity (%)	Specificity (%)
Rose *et al.*, 1999 [36]	11	100	100
Narayan *et al.*, 2001 [37]	24	83	92
Reinhardt *et al.*, 2001 [38]	35	91	100
Total	70	91	98

Table 4. — *PET scan detection of paraaortic nodal metastasis in cervical cancer. Surgicopathologic studies.*

Study (ref.)	n	Sensitivity (%)	Specificity (%)
Rose *et al.*, 1999 [36]	32	75	92
Yeh *et al.*, 2002 [39]	42	83	97
Lin *et al.*, 2003 [40]	50	86	94
Total	124	82	95

PET scanning has also been shown to accurately assess response to therapy in cancer patients, correctly detect early

recurrences and, ultimately, has prognostic value. Hence, PET scanning is being increasingly utilised in several malignancies, either squamous, glandular, mesenchymal, or haematological. PET scanning is becoming a widely available technology that is being used increasingly in the initial evaluation of cervical cancer, mainly in the assessment of nodal disease but also for detection of distant metastases. Whole-body PET scanning can accurately detect liver, bone and peritoneal metastases. A new generation of PET/CT hybrid scanners have been developed so that the metabolic abnormalities identified by PET may be anatomically localised by CT. The high cost of PET represents its principal limitation.

Management of patients with locally advanced cervical cancer

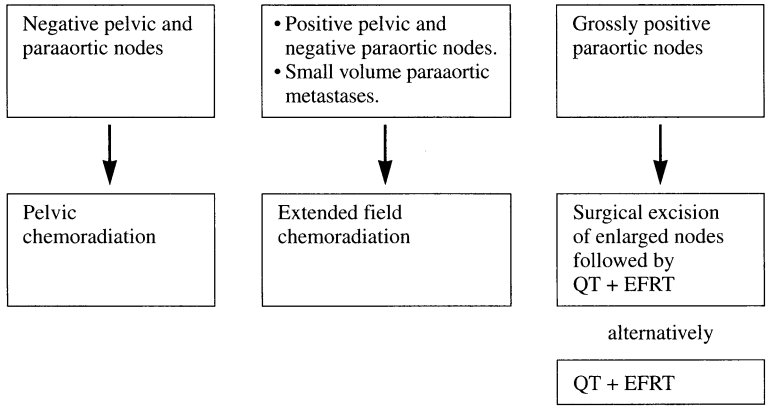
Taking all the previous data into account, we would like to conclude this paper by proposing that treatment strategies for locally advanced cervical cancer could be based on PET/CT findings. It should be emphasised though, that every one of the proposed therapeutic options should be subjected to randomised controlled trials.

Patients with negative pelvic and paraaortic nodes, as assessed by PET/CT imaging, could be offered pelvic irradiation with concurrent chemotherapy. It is undisputed that chemoradiation provides significantly better local control and survival in comparison to radiation alone [23].

It is conceivable that patients with metastatic pelvic and negative paraaortic nodes will benefit from the use of concomitant chemotherapy with prophylactic extended field radiotherapy to encompass the low para-aortic area, since this group of patients have a high risk of exhibiting microscopic paraaortic nodal disease (Table 5).

Similarly, patients with small volume paraaortic metastases could also be treated with extended field chemoradiation. It has been recognised in a GOG study [17] that this approach is feasible and confirmed that not every patient with paraaortic nodal metastases have systemic disease. In addition, Mutic and co-workers [24] have recently demonstrated that PET/CT-guided intensity modulated radiotherapy is feasible in this subset of patients afflicted with small volume paraaortic disease. It should be remembered that the complication rate attributed to extended field radiotherapy is considerably reduced in the absence of prior staging surgery [7, 25].

Table 5. — *Algorithm for the management of locally advanced cervical cancer (Stages IIB to IVA) based on PET/CT imaging.*



QT + EFRT = extended field chemoradiation.

Finally, two main therapeutic options can be offered to patients with grossly involved paraaortic nodes: surgical excision of the enlarged nodes followed by extended field chemoradiation, or avoid the surgical procedure, and use exclusively chemoradiotherapy (Table 5). Considering that radiotherapy cannot sterilise metastatic nodes larger than 2 cm in diameter [26] and that some retrospective data strongly suggest that excision of macroscopic nodes before commencement of radiotherapy converts the prognosis to that of patients with nodal micrometastases improving survival [14, 15], the removal of bulky nodes before chemoradiotherapy is recommended by some investigators. To reduce severe gastrointestinal, haematologic and genitourinary morbidity associated with extended field chemoradiation in patients having prior abdominal surgery, an extraperitoneal approach is recommended [27, 28], particularly an extraperitoneal laparoscopy. However, the role of laparoscopy in debulking involved lymph nodes is controversial and, even enthusiasts of this methodology like Dargent *et al.* [29], contraindicate laparoscopic lymphadenectomy because of the frequent unresectability (only about 45% of macroscopic nodes in Stage IIIB disease can be removed), risk of complications and the hazard of tumour dissemination.

The only published randomised trial, discussed above, demonstrated a detrimental effect of surgical staging on both progression-free and overall survival in comparison to clinical staging [19]. Since both pelvic nodes larger than 3 cm on CT or MRI, and CT-guided aspiration/biopsy positive para-aortic nodes were two exclusion criteria in this study, a clinical trial is still needed to assess the role of the surgical removal of bulky positive nodes. It is possible that a few selected individual patients could benefit from this approach. Meanwhile, many authorities prefer to offer to this group of patients extended field chemoradiation avoiding the risks inherent in the surgical procedure and the increased radiation-related morbidity after surgery. Moreover, this therapeutic option is unquestionable when there are contraindications to surgery and when the nodal disease is judged unresectable by different imaging modalities.

Since distant metastases are so frequent in locally advanced cervical cancer, in up to 60% of the cases [18], efforts should be made not only to improve the chemotherapy protocols but also to develop new molecular targeted therapies.

The optimal chemotherapy regimen is yet to be defined. Although single agent cisplatin concomitantly with radio-

therapy is widely used, it seems that the association of cytotoxic drugs could be more helpful. Ongoing randomised clinical trials in locally advanced cervical cancer are underway to evaluate the activity of newer radiosensitizers such as gemcitabine, paclitaxel, topotecan and tirapazamine. It is expected that the new standard chemoradiotherapy regimens for the treatment of locally advanced cervical cancer, in the near future, will include a combination of cisplatin plus another radiosensitizer, as preliminary reports strongly suggest.

Furthermore, other therapeutic approaches need to be thoroughly tested, such as: chemoradiation after neoadjuvant chemotherapy, neoadjuvant chemotherapy followed by radical surgery plus adjuvant chemoradiation, and preoperative chemoradiation. In every one of these three proposals, chemoradiation (investigational arm) would substitute for the classical use of radiotherapy alone. It is emphasised that more active drug combinations should be utilised in the chemotherapy protocols, instead of cisplatin alone. Nevertheless, it is probable that a significant increase in survival will not be obtained, even with the most optimal combination of radiotherapy, chemotherapy and surgery. Therefore, it is hoped that the enormous array of molecular targeted therapies in current development will assist in the improvement of both the quality of life and survival of patients with cervical cancer.

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