Contribution of pelvic and para-aortic lymphadenectomy with sentinel node biopsy in patients with IB2–IIB cervical cancer

E Chéreau*,1, J-G Feron1, M Ballester1, C Coutant1, C Bezu1, R Rouzier1, E Touboul2 and E Darai1

1Department of Gynecology-Obstetrics, Hôpital Tenon, Assistance Publique des Hôpitaux de Paris, CancerEst, Université Pierre et Marie Curie Paris 6, 4 rue de la Chine, Paris 75020, France; 2Department of Radiotherapy, Hôpital Tenon, Assistance Publique des Hôpitaux de Paris, CancerEst, Université Pierre et Marie Curie Paris 6, Paris 75020, France

OBJECTIVE: Detection of lymph node involvement in women with IB2–IIB cervical cancer could have a positive effect on survival. We set out to evaluate the incidence of pelvic and/or para-aortic lymph node involvement using the sentinel node (SN) biopsy and its impact on survival.

METHODS: From 2002 to 2010, 66 women with IB2–IIB cervical cancer underwent a pelvic and paraaortic lymphadenectomy with SN biopsy. Survival between groups according to lymph node status was evaluated.

RESULTS: Mean tumour size was 43.5 mm. At least one SN was detected in 69% of the 45 SN procedures performed. Sixteen of these patients had metastatic SN and the false negative rate was 20%. Metastatic pelvic SNs or non-SNs were detected in 33 patients (50%), including pelvic-positive nodes in 26 (40%), pelvic- and paraaortic-positive lymph nodes in seven (11%), and paraaortic skip metastases in two (6%). Positive paraaortic node was the sole determinant for disease-free survival (DFS) and overall survival (OS; P < 0.001). Differences in DFS and OS between groups according to the nodal status were observed (P < 0.001).

CONCLUSION: SN procedure gave a higher rate of metastasis detection. Further studies are required to evaluate whether pre-therapeutic node staging, including paraaortic and pelvic lymphadenectomy, should be performed.

British Journal of Cancer (2012) 106, 39–44. doi:10.1038/bjc.2011.541 www.bjcancer.com

© 2012 Cancer Research UK

Keywords: pelvic lymphadenectomy; paraaortic lymphadenectomy; locally advanced cervical cancer; sentinel node biopsy; survival

Despite a recent revision of the FIGO (International Federation of Gynecology and Obstetrics) classification, cervical cancer continues to be the only gynaecological malignancy that is not surgically staged (Petru et al, 2009). This contributes to difficulties in evaluating the effect of therapy, particularly of lymphadenectomy, on survival for locally advanced stages of cervical cancer (higher than or equal to stage IB2). Indeed, lymph node involvement is relatively frequent in locally advanced stages of cervical cancer and is a major determinant for adjuvant therapy (Zander et al, 1981; Shepherd, 1996; Morice and Castaigne, 2005).

Imaging techniques including CT, MRI and PET have a high diagnostic accuracy for evaluating enlarged lymph nodes, but a poor accuracy for regular-sized lymph nodes (Hricak et al, 1988; Kim et al, 1993, 1994; Subak et al, 1995; Boss et al, 2000; Sheu et al, 2001; Hertel et al, 2002; Narayan et al, 2003; Kamelle et al, 2004; Marnitz et al, 2005; Selman et al, 2008). Systematic lymphadenectomy is thus recommended to evaluate metastases in pelvic and/or para-aortic lymph nodes (PALNs) (Zander et al, 1981; Piver, 1984; Lanciano et al, 1991; Chu et al, 1997; Michel et al, 1998; Stryker and Mortel, 2000; Vergote et al, 2002; Narayan et al, 2003). Sentinel node (SN) biopsy has also become widespread to determine lymph node status in early stages of cervical cancer (Selman et al, 2008; Altgassen et al, 2009). However, the interest of the SN biopsy in locally advanced stages of cervical cancer is more debatable, because of the low SN detection rate and high false negatives (Barranger et al, 2003, 2004a, b; Coutant et al, 2007; Altgassen et al, 2009).

Although a prospective study has shown a survival disadvantage for patients following surgical staging compared with clinical staging when concurrent radiotherapy (CRC) is recommended (Lai et al, 2003), most authors agree that lymph node status should be assessed by systematic lymphadenectomy. However, a debate exists whether paraaortic lymphadenectomy alone is sufficient or whether a pelvic and paraaortic lymphadenectomy should be performed systematically. Leblanc et al (2007) recommended a paraaortic lymphadenectomy alone, considering that CRC possibly associated with localised boost on positive pelvic nodes and/or on the parametria are sufficient to control local regional disease. In contrast, Houvenaeghel et al (2006) demonstrated persistence of active pelvic lymph node metastases after CRC, and that pelvic lymphadenectomy could reduce the rate of lateropelvic recurrences whatever the PALN status.

Therefore, the aim of the present retrospective study was to evaluate the incidence of pelvic and/or PALN involvement, using both SN biopsy and systematic pelvic and paraaortic lymphadenectomy, and the impact on survival in women with advanced stages of cervical cancer (stage IB2 or II).
PATIENTS AND METHODS

Patients
From 2002 to 2010, 66 women with locally advanced cervical cancer corresponding to 1988 FIGO stage IR2 or II underwent a pre-therapeutic pelvic and paraaortic lymphadenectomy by laparoscopy in the gynaecology unit of Tenon Hospital, France (Barranger et al, 2003, 2004a,b; Coutant et al, 2007). All the women had biopsy-proven cervical cancer and had undergone pelvic MRI, and 45 of the 66 women had undergone a laparoscopic SN procedure before pelvic and paraaortic lymphadenectomy.

All women gave informed written consent to the therapeutic procedures and to the analysis of data related to their malignancy in accordance with institutional guidelines and the Declaration of Helsinki. The protocol was approved by the local Ethics Committee.

The medical records were reviewed to determine age, the body mass index, tumour stage, histology, tumour size on MRI, surgical procedure, intra- and postoperative complications, and the final pelvic and paraaortic node status. Outcome was obtained from the outpatient records.

The predictive factors for disease-free survival (DFS) and overall survival (OS) were analysed in univariate and multivariate analysis to provide survival data. Survival between groups according to their nodal histological status – positive or negative pelvic nodes and positive or negative paraaortic nodes – was evaluated.

Technique

SN procedure The SN procedure was performed as previously reported (Barranger et al, 2003; Coutant et al, 2007). The pelvic and lower paraaortic regions were carefully inspected by laparoscopy for lymph ducts and dye uptake by lymph nodes. All blue and/or hot lymph nodes were removed separately. The position of each SN relative to the major pelvic vessels, vena cava or aorta was recorded.

After the SN procedure, systematic transperitoneal lymph node dissection extending from the external iliac (and obturator nerve) to the level of the left renal vein was performed. The absence of residual pelvic or paraaortic radioactivity was verified before and after pelvic and paraaortic lymphadenectomy.

Lymph nodes with macroscopic metastases were sectioned. Normal-appearing SNs were cut perpendicular to the long axis. All SNs were submitted to intra-operative imprint cytology. Air-dried cytological smears were prepared by scraping the cut surfaces and staining with a rapid May–Grünewald–Giemsa method. Each half-SN was sectioned at 3-mm intervals. Each 3-mm section was analysed at four additional levels of 150 μm and four parallel sections; one was used for haematoxylin and eosin (H&E) staining, and H&E-negative sections were examined by immunohistochemistry (IHC) with an anticytokeratin antibody cocktail (cytokeratins AE1–AE3; Dako Corporation, Glostrup, Denmark). Non-SNs were submitted totally and blocked individually after 3-mm sectioning.

Macrometastases was defined by a single focus of metastatic disease per node measuring more than 2 mm, micrometastases as a focus of metastatic disease ranging from 0.2 mm to no more than 2 mm and, in accordance with previous studies (Marchiole et al, 2005; Bezu et al, 2010), submicrometastases as metastases measuring no more than 0.2 mm including the presence of a single non-cohesive tumour cell. SNs and non-SNs were considered positive when they contained macrometastases, micrometastases or submicrometastases.

Concurrent radiochemotherapy
External pelvic radiation therapy was given through four orthogonal fields: antero-posterior (AP) and postero-anterior (PA), and two lateral fields. The upper limit of the AP/PA field was L4–L5 interspace. The lower limit extended distally to the midpoint of the obturator foramen or the lowest level of disease with a 3-cm margin, and laterally 2 cm beyond the lateral margins of the bony pelvic wall. The upper and lower limits of the lateral fields were the same as those of the AP/PA field. The anterior limit of the lateral field was a horizontal line drawn at the anterior border of the pubic symphysis. The posterior limit of lateral field was placed at the S2–S3 interspace. Customised blocks were used to spare the anterior half of the rectum posteriorly and a proportion of small bowel anteriorly.

Pelvic radiation therapy consisted of 40 Gy, using 2.25 Gy per fraction, 4 days a week. A vaginal booster dose of 20 Gy was given at 5–6 weeks by means of brachytherapy. Brachytherapy was performed after radical hysterectomy when uterine catheterisation was impossible.

Concurrent chemotherapy was given during the 1st and 4th week of radiation therapy and consisted of a continuous 5-fluorouracil infusion (750 mg m⁻² per day) and a cisplatin bolus (20–25 mg m⁻² per day) 1 h before radiotherapy, for days 1, 2, 4 and 5. When the pelvic and paraaortic nodes were not involved, simple or radical laparoscopic hysterectomy was performed 6 weeks after the end of CRC. Women with positive lymph node involvement underwent a specific CRC regimen. For these women, the total dose of external radiotherapy delivered was 45 Gy with an iliac boost of 10 Gy, followed by the same brachytherapy regimen. The chemotherapy protocol was the same, but delivered the 1st and 5th week of irradiation.

Patients with positive aortic nodes received extended-field radiation up to the level of T12-L1. The lateral limits were set 4 cm from the midline.

Statistical analysis
Data were analysed using the χ²-test or the Fisher’s exact test and the Student’s t-test. Differences were considered significant when P < 0.05. OS time was calculated in months from the date of surgery to death, or the date of last follow-up for surviving patients and DFS time from the date of surgery to recurrence. The Kaplan–Meier method was used to estimate the survival distribution, and comparisons of survival were made by the use of the log-rank test. Cox proportional hazards regression was used for multivariate analysis. Informative prognostic factors for outcome were selected according to Akaike Information Criteria.

RESULTS

Epidemiological and surgical characteristics of the population

Patient and tumour characteristics are reported in Table 1. The mean tumour size was 43.5 mm (range: 12–70). Eighty-six percent of the patients had a squamous cell carcinoma. About half of the patients had a moderately or poorly differentiated carcinoma, and more than half of the patients had FIGO stage IIB.

All 66 patients underwent both pelvic and paraaortic lymphadenectomy for a cervical cancer. This procedure was followed by CRC and brachytherapy for 58 of them (88%). A total of 2 of the 66 patients required a conversion to laparotomy: for anaesthesiological disorders related to hypoventilation for one and for ureteral injury requiring a bladder reimplantation for the other. No bleeding or vascular injury requiring laparotomy was observed. Moreover, none of these patients had unresectable bulky nodes. Eight patients (12%) with stage II A cervical cancer and tumour size below 4 cm underwent a laparoscopic pelvic and paraaortic lymphadenectomy associated with a radical hysterectomy during the same surgical procedure, followed by CRC and brachytherapy.
Table 1 Epidemiological and surgical characteristics of the 66 patients with locally advanced stages of cervical cancers, who underwent pelvic and para-aortic lymphadenectomy and sentinel lymph node biopsy

| Characteristics                          | Patients (n = 66) |
|------------------------------------------|------------------|
| Mean age in years (range)                | 48.8 (28 – 76)   |
| Post-menopausal patients (%)             | 26 (39)          |
| Mean body mass index, kg m⁻² (range)     | 23.4 (16.8 – 35.0) |
| Mean tumour size on MRI, mm (range)      | 43.5 (12 – 70)   |
| Tumour location in the cervix            |                  |
| Ecto-cervical (%)                        | 62 (94)          |
| Endocervical (%)                         | 3 (5)            |
| Exo and endocervical (%)                 | 1 (1)            |
| Tumour histology                         |                  |
| Squamous cell carcinoma (%)              | 57 (86)          |
| Adenocarcinoma (%)                       | 9 (14)           |
| Histological grade of the tumour         |                  |
| Well differentiated (%)                  | 30 (45)          |
| Moderately differentiated (%)            | 10 (15)          |
| Poorly differentiated (%)                | 15 (23)          |
| Unclassified (%)                         | 11 (17)          |
| FIGO classification                      |                  |
| IB2 (%)                                  | 23 (34)          |
| IIA (%)                                  | 8 (12)           |
| IIB (%)                                  | 35 (54)          |
| Therapy associated with LPPAL            |                  |
| Chemoradiotherapy and brachytherapy (%)  | 27 (41)          |
| Chemoradiotherapy and brachytherapy, followed by hysterectomy (%) | 31 (47) |
| First radical hysterectomy and LPPAL, followed by chemoradiotherapy and brachytherapy (%) | 8 (12) |

Abbreviations: FIGO = International Federation of Gynecology and Obstetrics; LPPAL = laparoscopic pelvic and para-aortic lymphadenectomy; MRI = magnetic resonance imaging.

SN procedure

SN procedure was performed in 45 patients, resulting in the detection of at least one SN in 69% of cases (n = 31; Table 2). A bilateral SN was found in 26% of cases (n = 12). The mean number of SN removed was 2.1 (1 – 4) per patient. No difference in cervical cancer stages between patients with and without SN was detected.

Among these 45 patients, in 87% of cases (39 among 45 cases), SN was hot and blue, in 5 cases, SN was blue alone (11%) and in 1 case, SN was radioactive alone (2%).

Histology revealed metastatic SN in 16 patients (52%, 16 among 31 patients). SN was radioactive alone (2%), whereas 17% had only metastatic non-SNs. In patients with isolated pelvic positive nodes, 83% of them had both metastatic SNs and non-SNs, whereas 17% had only metastatic SNs. None had only metastatic non-SNs.

Four false negative cases of SN procedure were observed corresponding to patients with unilateral SN detection. In three of them, only one SN was removed and in the last case, two SNs were removed. The four patients also had positive PALNs.

Pelvic and para-aortic lymphadenectomy

The median number of lymph nodes removed, including SNs during pelvic or para-aortic lymphadenectomy, were 12.5 nodes (3 – 24) and 12.5 nodes (4 – 28), respectively. Metastatic pelvic SNs or non-SNs were detected in 33 patients (50%). Metastatic PALNs were detected in nine patients (14%). Skip metastases to PALNs were diagnosed in two patients in the presence of negative pelvic lymph nodes. In these two patients, the first presented 1-mm micrometastases with one negative SN identified (HES and IHC).

Pelvic and para-aortic lymphadenectomy with SN biopsy

The second patient did not have a SN biopsy and presented 10 pelvic nodes free from disease and one of the 28 PALNs involved. Among the 35 patients (53%) with positive nodes, 20% of them had both pelvic and paraaortic positive nodes, 74% had only pelvic positive nodes and 6% had isolated paraaortic positives nodes. In patients with isolated pelvic positive nodes, 83% of them had both metastatic SNs and non-SNs, whereas 17% had only metastatic SNs. None had only metastatic non-SNs.

Four false negative cases of SN procedure were observed corresponding to patients with unilateral SN detection. In three of them, only one SN was removed and in the last case, two SNs were removed. The four patients also had positive PALNs.

OS and DFS

The median follow-up was 28.3 months (2 – 79 months; Figures 1 and 2). Seven of the sixty-six patients (11%) relapsed, including three centropelvic recurrences (two of three in patients without hysterectomy), two peritoneal carcinomatosis (11 and 17 months after surgery), one lateropelvic and one common iliac node recurrences. The 5-year DFS was 86% and the 5-year OS was 78%. Univariable analysis for DFS found that the only significant factor was the positivity of paraaortic nodes (P<0.001). This factor was...
Pelvic and para-aortic lymphadenectomy with SN biopsy
E Chéreau et al

Clinical Studies

42

Figure 1 Disease-free survival according to nodal status in 66 patients with stage Ib2–IIB cervical cancer. *No significant difference in survival between patients with negative pelvic and paraaortic nodes and patients with positive pelvic nodes and negative paraaortic nodes.

Figure 2 Overall survival according to nodal status in 66 patients with stage Ib2–IIB cervical cancer. *No significant difference in survival between patients with negative pelvic and paraaortic nodes and patients with positive pelvic nodes and negative paraaortic nodes patients.

also significant in multivariable analysis (P = 0.02). For OS, positive paraaortic nodes (P < 0.0001) remained the sole determinant factor in univariable, but not in multivariable analysis (Table 3).

The OS and PFS of the patients were assessed in three groups: no lymphatic disease, only pelvic-positive nodes and paraaortic-positives nodes. For both DFS and OS, we found statistical differences between these groups with a P-value < 0.001 (Figures 1 and 2).

DISCUSSION

The present study demonstrates the high incidence of pelvic and PALN involvement and the contribution of the SN biopsy to detect micrometastases in patients with locally advanced stages of cervical cancer.

A recent meta-analysis (Chemoradiotherapy for Cervical Cancer Meta-analysis Collaboration (CCCMAC), 2010) including 13 trials has confirmed that the gold standard to treat patients with locally advanced-stages cervical cancer is CRC: a 6% improvement in 5-year survival with chemoradiotherapy (hazard ratio = 0.81, P < 0.001) was observed when chemoradiotherapy was compared with the same radiotherapy. However, this meta-analysis based on lymph node status, especially iliac node involvement, was not completed as there were insufficient data not allowing to state on the impact of lymphadenectomy. We observed a high incidence of pelvic and PALN involvement, 50% and 14%, respectively, in our study. However, despite a significant difference in both OS and PFS between patients with positive pelvic and paraaortic positive nodes, and patients with only positive pelvic nodes, we cannot conclude that lymphadenectomy has a therapeutic effect, as no difference was observed between patients with and without positive pelvic lymph nodes. This explains why some authors recommend paraaortic lymphadenectomy only (preferentially by retroperitoneal approach) to determine the extent of radiotherapy while limiting the side effects on small bowel, suggesting that adjuvant chemoradiation is able to sterilise all pelvic lymph nodes in patients with locally advanced-stages cervical cancer. However, Houvenaeghel et al (2006) found that 16% of women with locally advanced cervical cancer initially treated by CRC had persistent positive pelvic lymph nodes. In a series of 73 patients with IB2–IIB cervical cancer treated by CRC, followed by paraaortic lymphadenectomy associated with pelvic lymphadenectomy or pelvic lymph node sampling in 36 patients, Morice et al (2007) reported that 13 patients (36%) had persistent positive pelvic lymph node after CRC. In the study of Morice et al (2007), among the four pelvic lymph node relapses, three occurred in patients who had not undergone pelvic lymphadenectomy. Moreover, in a multivariate analysis, Rouzier et al (2005) demonstrated that, in addition to tumour size, the main determinant of pelvic relapse was pelvic lymph node involvement. Therefore, in addition to prognostic relevance, pelvic lymphadenectomy may have a therapeutic impact by reducing the risk of lymph node relapse, thus reinforcing the idea that when lymphadenectomy is indicated before CRC, both pelvic and paraaortic lymphadenectomy should be performed. Indeed, Marnitz et al (2005) showed that removal of positive pelvic and/or positive PALNs was associated with significant improvement in OS, confirming that lymphadenectomy should be performed before primary chemoradiation. Comparing survival of patients undergoing negative PALN identified by surgical staging to patients with only radiographic exclusion of PALN metastases, Gold et al (2008) showed that patients with radiographic evaluation only had a poorer prognosis supporting the therapeutic effect of lymphadenectomy. Moreover, Tseng et al (2010) built a nomogram in patients with locally advanced-stage cervical cancer, showing a high heterogeneity in predicting death, but underlined the preponderant impact of both pelvic and paraaortic involvement. Finally, our results underline that three-quarters of patients with lymph node metastases were located in the pelvis, whereas only 20% had pelvic and paraaortic involvement, and only 6% had isolated paraaortic metastases. These data are of particular relevance, as two trials included in a recent meta-analysis (Lukka et al, 2002; Green et al, 2005; Chemoradiotherapy for Cervical Cancer Meta-analysis Collaboration (CCCMAC), 2010) showed greater benefits of adding chemotherapy after CRC, with

Table 3 Univariable and multivariable analysis of potential predictive factors of pelvic or para-aortic lymph node metastasis in 42 patients with stage Ib2–IIB cervical cancer

| Pelvic lymph node metastases | Para-aortic lymph node metastases |
|-----------------------------|----------------------------------|
| Tumour size                 | Univariable analysis (P)         |
| > 30 mm                     | 0.81                             |
| > 40 mm                     | 0.38                             |
| FIGO stage                  | 0.01                             |
| Post-menopausal status      | 0.44                             |
| Age                         | 0.12                             |
| Histology                   | 0.15                             |

Abbreviation: FIGO = International Federation of Gynecology and Obstetrics
an absolute improvement of 19% at 5 years. Patients with lymph
node involvement, especially with pelvic and/or paraaortic
metastases, could be good candidates for this new regimen.

Our SN detection is low compared with those observed in
patients with early stages of cervical cancer (Plante et al., 2003;
Martinez-Palones et al., 2004; Coutant et al., 2007), but concur with
those of previous studies on SN in locally advanced stages of
cervical cancer (Coutant et al., 2007). This difference in detection
rates may be explained by the obstruction of lymphatic vessels by
tumour embols. Moreover, we found a high false negative rate of
20% in the present study, contrasting with that of Altgassen et al.
(2009) reporting a false negative rate under 10% for tumour size
below 2 cm for early stages of cervical cancer. All these
considerations underline that SN procedure cannot be considered
an alternative to lymphadenectomy in patients with locally
advanced stages of cervical cancer. Despite a low SN detection
and a high false negative rate, our results underline the
contribution of ultrastaging, using combined serial sectioning
and IHC to detect micrometastases; 20% of our patients with
lymph node involvement were exclusively diagnosed as a result of
ultrastaging. Lentz et al. (2004), using IHC without serial
sectioning, detected micrometastases in 19 out of a series of 132
women with 3106 negative lymph nodes on routine histology (15%;
95% confidence interval: 9–22%). Silva et al. (2005) confirmed the
contribution of IHC in detecting micrometastases in 5 of 98
negative SNs. In a recent review on SN biopsy in cervical cancer,
using H&E and IHC (Lambaudie et al., 2003; Martinez-Palones
et al., 2004; Niikura et al., 2004; Kraft et al., 2006) on SNs, no
micrometastases were detected. Using H&E, serial sectioning and
IHC, the incidence of micrometastases ranged from 0% to
47.4% with a mean value of 28.3%, similar to that observed in
the current study.

From a clinical view point, Juretzka et al. (2004) first underlined
the potential prognostic relevance of micrometastases and
recommended adjuvant therapy for these patients. In a case–
control study, Marchiolle et al. (2005) found that the relative risk of
recurrence in the presence of true micrometastases (focus of
metastatic disease ranging from 0.2 mm to no more than 2 mm)
was 2.30 (confidence interval: 1.65–3.20, P < 0.01). Moreover, in
series of 894 patients, Horn et al. (2008) confirmed the prognostic
relevance of detecting micrometastases with a correlation between
their presence and the risk of recurrence. Hence, all these data
reinforce the notion that patients with metastases, including those
with micrometastases detected in SNs, could be candidates for
adjuvant chemotherapy after CRC.

Some limitations of the present study have to be underlined.
First, the retrospective nature of the study cannot exclude the risk
of potential bias. Second, no difference was observed between
patients with and without positive pelvic lymph nodes, raising
the issue on the rational of systematic pelvic lymphadenectomy.
However, this could be explained by both the sample size of the
study and the relatively short follow-up with few events (seven
recurrences). Concerning the rational for completion of the surgery
in our protocol, it is clear that no consensus exists on its
indication and on its impact on survival while exposing patients
to the risk of potential severe postoperative complications. Third,
despite the contribution of ultrastaging using combined serial
sectioning and IHC to detect micrometastases, our study was
unable to prove the therapeutic effect of pelvic lymphadenectomy.
This could suggest that pre-therapeutic pelvic lymphadenectomy is
unnecessary, as pelvic radiotherapy could be sufficiently effective
on positive pelvic nodes. However, even in new regimens of
radiotherapy or chemoradiation, there is a lack of data on pelvic
node sterilisation, particularly, when using radiotherapy boost
(Haie-Meder et al., 2009).

CONCLUSION
The SN procedure resulted in an increased detection rate of pelvic
node metastases, which are often underestimated, despite a high
false negative rate. According to a recent meta-analysis showing
the benefits of adding chemotherapy after CRC in case of lymph
node metastases, patients with lymph node metastases could be
good candidates for this regimen. Further studies are required to
evaluate whether pre-therapeutic node staging, including para-
aortic and pelvic lymphadenectomy, should be performed in
women with locally advanced cervical cancer.

REFERENCES
Altgassen C, Muller N, Hornemann A, Kavallaris A, Hornung D, Diedrich
K, Jarutat T (2009) Immunohistochemical workup of sentinel nodes in
endometrial cancer improves diagnostic accuracy. Gynecol Oncol 114(2):
284–287
Barranger E, Cortez A, Commo F, Marpeau O, Uzan S, Darai E, Callard P
(2004a) Histopathological validation of the sentinel node concept in
cervical cancer. Ann Oncol 15(6): 870–874
Barranger E, Cortez A, Uzan S, Callard P, Darai E (2004b) Value of
Barranger E, Cortez A, Uzan S, Darai E, Callard P
Barranger E, Grahek D, Cortez A, Talbot JN, Uzan S, Darai E (2004)
Histopathological validation of the sentinel node concept in cervical cancer.
Ann Oncol 15(6): 870–874
Barranger E, Cortez A, Uzan S, Callard P, Darai E (2004b) Value of
Barranger E, Grahek D, Cortez A, Talbot JN, Uzan S, Darai E (2003)
Laparoscopic sentinel lymph node procedure using a combination of
patent blue and radioisotope in women with cervical carcinoma. Cancer
97(12): 3003–3009
Bezu C, Coutant C, Ballester M, Feron JG, Rouzier R, Uzan S, Darai E (2010)
Ultrastaging of lymph node in uterine carcinomas. J Exp Clin Cancer Res 29:
5 Boss EA, Barentsz JO, Massuger LF, Boonstra H (2000) The role of MR
imaging in invasive cervical carcinoma. Eur Radiol 10(2): 256–270
Che´reau P, Gonzague-Casabianca L (2006) Residual pelvic lymph node involve-
cent infection among Chinese. Gynecol Oncol 84(1): 49–53
Coutant C, Morel O, Delpech Y, Uzan S, Darai E, Barranger E (2007)
Laparoscopic sentinel node biopsy in cervical cancer using a combined
detection: 5-years experience. Ann Surg Oncol 14(8): 2392–2399
Gold MA, Tian C, Whitney CW, Rose PG, Lanciano R (2008) Surgical vs
radiographic determination of para-aortic lymph node metastases before
chemoradiation for locally advanced cervical carcinoma: a Gynecologic
Oncology Group Study. Cancer 112(9): 1954–1963
Green J, Kirwan J, Tierney J, Vale C, Symonds P, Fresco L, Williams C,
Collingwood M (2005) Concomitant chemotherapy and radiation therapy
for cancer of the uterine cervix. Cochrane Database Syst Rev (3):
CD005225
Haie-Meder C, Morice P, Castiglione M (2009) Cervical cancer: ESMO
clinical recommendations for diagnosis, treatment and follow-up. Ann
Oncol 20(Suppl 4): 27–28
Hertel H, Kohler C, Elhawary T, Michels W, Possover M, Schneider A
(2002) Laparoscopic staging compared with imaging techniques in the
staging of advanced cervical cancer. Gynecol Oncol 87(1): 46–51
Horn LC, Hentschel B, Fischer U, Peter D, Bilek K (2008) Detection of
micrometastases in pelvic lymph nodes in patients with carcinoma of
the cervix uteri using step sectioning: Frequency, topographic distribution
and prognostic impact. Gynecol Oncol 111(2): 276–281
Houvenaeghel G, Lelievre L, Pigaud AL, Buttarelli M, Jacquemier J, Viens
P, Gonzalez-Casabianca L (2006) Residual pelvic lymph node involve-
melting in cervical cancer. Gynecol Oncol 102(1): 74–79

© 2012 Cancer Research UK
British Journal of Cancer (2012) 106(1), 39–44

Clinical Studies
Hricak H, Lacey CG, Sandles LG, Chang YC, Winkler ML, Stern JL (1988) Invasive cervical carcinoma: comparison of MR imaging and surgical findings. *Radiology* 166(3): 623–631

Juretzka MM, Jensen KC, Longacre TA, Teng NN, Hussain A (2004) Detection of pelvic lymph node micrometastasis in stage IA2-IB2 cervical cancer by immunohistochemical analysis. *Gynecol Oncol* 93(1): 107 – 111

Kamelle SA, Rutledge TL, Tillmanns TD, Gould NS, Cohn DE, Wright J, Herzog TJ, Rader JS, Gold MA, Johnson GA, Walker JL, Mannel RS, McMeekin DS (2004) Surgical-pathological predictors of disease-free survival and risk groupings for IB2 cervical cancer: do the traditional models still apply? *Gynecol Oncol* 94(2): 249 – 255

Kim SH, Choi BI, Han JK, Kim HD, Lee HP, Kang SB, Lee FY, Han MC (1993) Preoperative staging of uterine cervical carcinoma: comparison of CT and MRI in 99 patients. *J Comput Assist Tomogr* 17(4): 633 – 640

Kim SH, Kim SC, Choi BI, Han MC (1994) Uterine cervical carcinoma: evaluation of pelvic lymph node metastasis with MR imaging. *Radiology* 190(3): 807 – 811

Kraft O, Sevick L, Klat J, Koliba P, Curik R, Kroizova H (2006) Detection of sentinel lymph nodes in cervical cancer. A comparison of two protocols. *Nucl Med Rev Cent East Eur* 9(1): 65 – 68

Lai CH, Huang KG, Hong JH, Lee CL, Chou HH, Chang TC, Hsieh S, Huang HJ, Ng KK, Tsai CS (2003) Randomized trial of surgical staging (extraperitoneal or laparoscopic) vs clinical staging in locally advanced cervical cancer. *Gynecol Oncol* 89(1): 160 – 167

Lambaudie E, Collinet P, Narducci F, Sonoda Y, Papageorgiou T, Carpenter P, Leblanc E, Queruel D (2003) Laparoscopic identification of sentinel lymph nodes in early stage cervical cancer: prospective study using a combination of patent blue dye injection and technetium radiocolloid injection. *Gynecol Oncol* 89(1): 84 – 87

Lanciano RM, Martz K, Coia LR, Hanks GE (1991) Tumor and treatment. *Int J Radiat Oncol Biol Phys* 20(1): 95 – 106

Leblanc E, Narducci F, Frumovitz M, Lesoan A, Castelain B, Baranzelli MC, Taieb S, Fournier C, Querel D (2007) Therapeutic value of pretherapeutic extraperitoneal laparoscopic staging of locally advanced cervical carcinoma. *Gynecol Oncol* 105(2): 304 – 311

Lentz SE, Madersbacher LI, Felix JC, Ye W, Groshen S, Amezcua CA (2004) Identification of micrometastases in histologically negative lymph nodes of early-stage cervical cancer patients. *Obstet Gynecol* 103(6): 1204 – 1210

Lukka H, Hirte H, Fyles A, Thomas G, Elit L, Johnston M, Fung MF, Browman G (2002) Concurrent cisplatin-based chemotherapy plus radiotherapy for cervical cancer – a meta-analysis. *Clin Oncol (R Coll Radiol)* 14(3): 203 – 212

Marchiolo P, Buener A, Benchab M, Nezhat K, Dargent D, Mathévet P (2005) Clinical significance of lympho vascular space involvement and lymph node micrometastases in early-stage cervical cancer: a retrospective case-control surgico-pathological study. *Gynecol Oncol* 97(3): 727 – 732

Marnitz S, Kohler C, Roth C, Fuller J, Hinkelbein W, Schneider A (2005) Is there a benefit of pretreatment laparoscopic transperitoneal surgical staging in patients with advanced cervical cancer? *Gynecol Oncol* 95(2): 536 – 544

Martinez-Palones JM, Gil-Moreno A, Perez-Benavente MA, Roca I, Xercavins J (2004) Intraoperative sentinel node identification in early stage cervical cancer using a combination of radiolabeled albumin injection and isosulfan blue dye injection. *Gynecol Oncol* 92(3): 845 – 850

Michel G, Morice P, Castaigne D, Leblanc M, Rey A, Duvillard P (1998) Lymphatic spread in stage Ib and II cervical carcinoma: anatomy and surgical implications. *Obstet Gynecol* 91(3): 360 – 363

Morice P, Castaigne D (2005) Advances in the surgical management of invasive cervical cancer. *Curr Opin Obstet Gynecol* 17(1): 5 – 12

Morice P, Uzan C, Zafrani Y, Delpech Y, Gouy S, Haie-Meder C (2007) The role of surgery after chemoradiation therapy and brachytherapy for stage IB2/II cervical cancer. *Gynecol Oncol* 107(1 Suppl 1): S122 – S124

Narayan K, McKenzie AF, Hicks RJ, Fisher R, Bernshaw D, Bau S (2003) Sentinel lymph node metastases in cervical cancer patients referred for radiotherapy. *Int J Gynecol Cancer* 13(5): 657 – 663

Nikura H, Okamura C, Akahira J, Takano T, Ito K, Okamura K, Yaehashi N (2004) Sentinel lymph node detection in early cervical cancer with combination 99mTc phytate and patent blue. *Gynecol Oncol* 94(2): 528 – 532

Petru E, Luck H, Stuart G, Gaffney D, Millan D, Vergote I (2009) Gynecologic Cancer Intergroup (GCCG) proposals for changes of the current FIGO staging system. *Eur J Obstet Gynecol Reprod Biol* 143(2): 69 – 74

Piver MS (1984) Extended field irradiation in the treatment of patients with cervical carcinoma involving biopsy proven para-aortic nodes. *Int J Radiat Oncol Biol Phys* 10(1): 193 – 1994

Plante M, Renaud MC, Tetr B, Harel F, Roy M (2003) Laparoscopic sentinel node mapping in early-stage cervical cancer. *Gynecol Oncol* 91(3): 494 – 503

Rouzier R, Morice P, De Crevoisier R, Pomel C, Rey A, Bonnet K, Recoules-Arche A, Duvillard P, Lhomme C, Haie-Meder C, Castaigne D (2005) Survival in cervix cancer patients treated with radiotherapy followed by radical surgery. *Eur J Surg Oncol* 31(4): 424 – 433

Selman TJ, Mann C, Zamora J, Appleyard TL, Khan K (2008) Diagnostic accuracy of tests for lymph node status in primary cervical cancer: a systematic review and meta-analysis. *CMAJ* 178(7): 855 – 862

Shepherd JH (1996) Cervical and vulva cancer: changes in FIGO definitions of staging. *Br J Obstet Gynaecol* 103(5): 405 – 406

Sheu MH, Chang CY, Wang JH, Yen MS (2001) Preoperative staging of cervical carcinoma with MR imaging: a reappraisal of diagnostic accuracy and pitfalls. *Eur Radiol* 11(9): 1828 – 1833

Silva LB, Silva-Filho AL, Traimian P, Trignelli SA, de Lima CF, Siqueira CF, Barroso A, Rossi TM, Pedrosa MS, Miranda D, Melo JR (2005) Sentinel node detection in cervical cancer with 99mTc-phytate. *Gynecol Oncol* 97(2): 588 – 595

Stryker JA, Mortel R (2000) Survival following extended field irradiation in carcinoma of cervix metastatic to para-aortic lymph nodes. *Gynecol Oncol* 79(3): 399 – 405

Subak LL, Hricak H, Powell CB, Azizi L, Stern JL (1995) Cervical carcinoma: computed tomography and magnetic resonance imaging for preoperative staging. *Obstet Gynecol* 86(1): 43 – 50

Tseng JY, Yen MS, Tsai NF, Lai CR, Horng HC, Tseng CC, Chao KC, Juang CM (2010) Prognostic nomogram for overall survival in stage IIIb-IVA cervical cancer patients treated with concurrent chemoradiation therapy. *Am J Obstet Gynecol* 202(2): 174.e1 – 174.e7

Vergote I, Amant F, Berteloot P, Van Gamma R, Scember D, Low S (2012) Laparoscopic robotic-assisted robotic surgery for advanced cervical cancer. *Br J Obstet Gynaecol* 119(7): 752 – 759

This work is published under the standard license to publish agreement. After 12 months the work will become freely available and the license terms will switch to a Creative Commons Attribution-NonCommercial-Share Alike 3.0 Unported License.