Tailoring the Field and Indication of Adjuvant Pelvic Radiation for Patients with FIGO Stage Ib Lymph Nodes-Negative Cervical Carcinoma Following Radical Surgery Based on the GOG Score – A Pilot Study

MN Rushdan,[1,2] *MD (UKM), MOG (UKM)*, EH Tay,[2] *MRCOG (UK), M Med (O&G), DGO (RANZCOG)*, HS Khoo-Tan,[3] *MBBS, FRCR*, KM Lee,[3] *FRCR (UK), FFR (Dublin), FAMS*, JH Low,[2] *MRCOG (UK), M Med (O&G), FAMS*, TH Ho,[2] *FRCOG (UK), FAMS*, KL Yam,[2] *MRCOG, M Med (O&G), FAMS*

Abstract

Introduction: The traditional indications for adjuvant pelvic radiotherapy (RT) for International Federation of Obstetrics and Gynecology (FIGO) stage Ib1 lymph nodes-negative cervix carcinoma following radical surgery based on histopathological factors, such as deep stromal invasion and lymphovascular space invasion (LVSI), were often inconsistently applied. The perceived risk of relapse was subjectively determined. This pilot study attempts to determine if the treatment outcome will be affected when the indication for RT is based on the Gynecologic Oncology Group (GOG) Risk Score (RS) and the field of adjuvant RT is tailored to the RS. Materials and Methods: From 1997 to 1999, 55 patients with FIGO stage Ib1 lymph nodes-negative cervical carcinoma limited to the cervix were prescribed RT following radical surgery, based on their RS, as follows: RS ≤40, RT is omitted; RS >40 to ≤120, modified (smaller) field RT; and RS >120, standard field pelvic RT. Their incidence and site of recurrence were compared with a similar cohort of 40 patients who were treated prior to 1997. Results: Prior to 1997, of the 40 patients, 10 patients were given standard field RT. There were 2 (5%) recurrent diseases. The mean duration of follow-up was 61.6 months (range, 1 to 103 months). The RS of 23 of the 30 patients who were not given RT were available. The mean RS was 22 with 5 patients having a score of >40. From 1997 onwards, of the 55 patients, 28 (51%) did not require RT, 13 (23%) were treated with modified (smaller) field RT and 14 (26%) were given standard field RT. There were 2 (3.6%) cases of relapse. The mean duration of follow-up was 36.4 months (range, 5 to 60 months). All patients with a RS of <40 did not suffer any relapse. Their survival outcomes were better when compared to patients who did not have any RT in the GOG Study. Conclusions: The results of this study indicated that postoperative adjuvant RT given to patients with a high GOG RS of >120, significantly improved their 5-year recurrence rate and disease-free survival, as compared with the similar group of patients who were without adjuvant therapy in the GOG study. Patients with a GOG risk-score of <40 may be safely spared from adjuvant pelvic RT. The current treatment protocol did not compromise the outcome in patients, compared with the use of a less precise treatment protocol in the past.

Ann Acad Med Singapore 2004;33:467-72

Key words: Cervix, Modified field, Radiotherapy, Small field, Wertheim's hysterectomy

Introduction

Although no significant survival difference exists between primary surgery and radiotherapy (RT) for the treatment of FIGO stage Ib cervical cancer, radical surgery is the preferred modality of treatment as conservation of the ovarian and vaginal function is of prime importance.[1-4] It also allows the study of prognostic histopathological factors, indicating the risk of treatment failure. Conventionally, patients deemed to be at a high risk of recurrence are given adjuvant therapy with the intention of improving their outcome, although its

[1] Department of O & G
Hospital Alor Star, Kedah, Malaysia
[2] Gynaecological Oncology Unit
KK Women's & Children's Hospital, Singapore
[3] Therapeutic Radiology Department
National Cancer Centre, Singapore
Address for Reprints: Dr E H Tay, Gynaecological Oncology Unit, KK Women's & Children's Hospital, 100 Bukit Timah Road, Singapore 229899.

contribution to improved survival is controversial. Patients with lymph nodes involvement, parametrial invasion and positive surgical margins,[5-14] are usually given postoperative adjuvant therapy. For patients without these risk factors, which account for half of total early-stage cervical cancer recurrences,[15] the traditional indications for postoperative adjuvant pelvic RT include large clinical tumour size, deep cervical stromal invasion and the presence of lymphovascular space invasion (LVSI).[5,9,14] However, such indications were often subjective and inconsistently applied.

The study by the Gynecologic Oncology Group (GOG)[5] had shown that in patients with negative nodes, but have a combination of these factors, the 3-year risk of recurrence could be as high as 41%.[5] A prognostic risk score (RS) using the clinical tumour size, LVSI and fractional depth of tumour invasion classified patients into low- (RS <40), intermediate- (RS 40 to 120) and high-risk group (RS >120). A RS >120 is correlated with a 41% risk of recurrence, while the intermediate-risk group has a 20% risk of recurrence.[5] Therefore, it may be justifiable to give patients in the moderate- and high-risk groups adjuvant therapy after surgery.

Since 1997, we have standardised the indication for postoperative adjuvant RT for patients with FIGO stage Ib cervical cancers, who were found to have diseases confined to the cervix, negative lymph nodes, negative surgical margins and negative parametrial invasion following radical surgery, by employing the prognostic scoring system described above.

As a large majority (87%) of recurrences occur at the vaginal vault and paravaginal tissue,[15] patients with intermediate RS may be treated with a reduced field of RT, with the aim to reduce RT-related morbidity.[1,15-17] A smaller field pelvic radiation was shown to have significantly less major complications than standard field RT, without affecting the clinical outcome.[15] Patients in the high-risk group will be treated with the standard field RT.

This pilot study aims to determine the patient outcome using this treatment approach and the safety and efficacy of a modified (small) field RT.

Materials and Methods

This is a prospective study involving all patients with FIGO stage Ib cervical carcinoma diagnosed and treated at the Gynaecological Cancer Centre (GCC) in KK Women's & Children's Hospital (KKH), Singapore, between January 1997 and December 1999. All patients were treated by Piver class 3 radical hysterectomy and pelvic lymphadenectomy.[18] Patients with histopathological findings that showed clear surgical margins, negative parametrial invasion and negative lymph nodes were included in the study. All histopathological results were presented and evaluated at our weekly Tumour Board meeting.

Since 1997, our centre has instituted a protocol for the indications and field of postoperative adjuvant RT based on the GOG RS. Patients were categorised into low-risk (RS <40), intermediate-risk (RS 40 to 120) and high-risk (RS >120) groups according to the GOG prognostic scoring system.[5] Patients with a low RS would not be given any adjuvant therapy. Our standard postoperative pelvic RT includes external beam RT and vaginal brachytherapy. The external beam pelvic RT is given using a 3-field technique to a total dose of 45 Gy in 25 fractions over 5 weeks. This is followed by vaginal vault brachytherapy, given in 2 fractions of 5 Gy each, prescribed to 0.5 cm from the surface of the vaginal cylindrical applicator using a high-dose rate technique. Patients with an intermediate RS were given a smaller modified field pelvic RT, where there is a reduction in the superior (lower sacroiliac joint) and lateral borders (1.5 cm inside the pelvic sidewall) to avoid irradiating the iliac chain of lymphatic channels. Those with a high RS received standard field pelvic RT.

Incomplete case records, patients who defaulted or who did not comply with the prescribed treatment were excluded. We analysed the data of patients treated between 1993 and 1996 (before the implementation of the current management protocol) and compared the results with that of patients treated in the period 1997 to 1999. Their complete histopathological reports were re-evaluated and retrospective re-scoring was done based on similar criteria.[5] RT-related complications and toxicity were analysed using the French-Italian glossary of complications.[19] The sites of recurrence, clinical presentation and disease-free intervals were documented in patients who developed recurrence of disease. The Kaplan and Meier[20] survival curves for the various categories of patients were compared using the log-rank test.

Results

There were 275 cases of FIGO stage Ib cervical carcinoma treated at our centre from January 1993 to December 1999; 140 cases were treated between January 1993 and December 1996 (4 years), and 135 cases were treated from January 1997 to December 1999 (3 years). Thirty-five (12.7%) patients had FIGO stage Ib2 diseases. Table 1 shows their treatment and histopathological outcomes and Table 2 denotes the characteristics of the patients and their diseases.

Ten (25%) patients had postoperative standard field RT, while 30 (75%) patients did not. The main indications for adjuvant RT were LVSI and/or deep stromal invasion in 7 out of 10 cases.

Based on histopathological reports, we were able to calculate the GOG RS for 33 patients: 23 in the surgery-only group and 10 cases in the adjuvant RT group (Table 1).

In the surgery-only group, the mean GOG RS was 22.3 and 5 patients had scores of >40. The mean GOG RS for patients who had adjuvant RT was 66. One had a score of <40 and 2 had >120. Based on the current indication criteria using the GOG risk scoring system, 14 patients, instead of 10, would have been given adjuvant RT.

The mean follow-up period was 61.6 months; 59.7 months (range, 1 to 103 months) in the surgery-only group and 74.3 months (range, 56 to 92 months) in the RT group.

Of the 60 patients who had negative lymph node, free surgical margin and no parametrial invasion on histology, 5 were excluded from the study because of default and failure to comply with the treatment protocol. For the 55 patients included in the study, 28 (51%) did not have adjuvant RT, 13 (23%) had modified (small) field RT and 14 (26%) were given standard field RT. Their mean GOG RS are shown in Table 1.

Table 1. Treatment of Patients with FIGO Stage Ib Cervical Carcinoma

Variable	1993 to 1996 (n = 140)	1997 to 1999 (n = 135)
Primary radical surgery	88 (63%)	92 (68%)
Negative lymph node, clear margin and parametrium	40	60*
No RT	30 (75%)	28 (51%)
Mean GOG RS	22.3 (1-147)†	9 (1-35.5)
Small field RT	-	13 (23%)
Mean GOG RS		65 (41-75)
Standard field RT	10 (25%)	14 (26%)
Mean GOG RS	65 (1.7-156.6)‡	169 (123-306)

FIGO: Internationational Federation of Obstetrics and Gynecology; GOG: Gynecologic Oncology Group; RS: risk score; RT: radiotherapy

* include 5 default cases

† calculation based on 23/30 cases

‡ calculation based on 10/10 cases

Table 2. Patients' Characteristics

Variable	1993 to 1996 (n = 40)	1997 to 1999 (n = 55)
Ethnic race		
Chinese	35 (87.5%)	50 (91%)
Malay	1 (2.5%)	5 (9%)
Indian	2 (5%)	0 -
Others	2 (5%)	0 -
Age (years)		
21-30	2 (5%)	1 (2%)
31-50	28 (70%)	33 (60%)
51-70	10 (25%)	21 (38%)
Mean tumour size (cm)	2.1	-
Histological type		
Squamous cell carcinoma	29 (72%)	35 (64%)
Adenocarcinoma	11 (28%)	17 (31%)
Adenosquamous carcinoma	-	3 (5%)
Histological grade		
1	11 (28%)	20 (36%)
2	20 (50%)	22 (40%)
3	9 (22%)	13 (24%)

The mean follow-up period was 36.4 months (range, 5 to 60 months); 34.6 months (range, 5 to 50 months) in the surgery-alone group, 35 months (range, 6 to 54 months) in the modified (small) field RT group and 38.6 months (range, 25 to 60 months) in the standard field RT group.

Overall, including those with positive lymph nodes/ surgical margin/parametrium, postoperative RT was given to 64% (59/92) of patients treated surgically.

RT-related morbidity was graded using the French-Italian glossary of complications (Table 3).[20] The morbidity was compared between small field and standard field RT. There was no grades 3 and 4 radiation morbidity in both groups.

Lymphoedema was the most common complication in the small field RT group, but are mild in severity. In the standard field RT group, minor rectal symptom, mainly per-rectal bleeding, was the most common complication encountered. The overall morbidity in both groups is minor and required only a short course of treatment.

Survival and Disease-free Survival

Between 1993 and 1996, there were 2 (5%) recurrences. Their disease-free interval was 57 months and 40 months, respectively. The first patient had extra-pelvic recurrences involving the para-aortic lymph nodes, lung and liver. She died of the disease 6 months after diagnosis. The second patient had local vaginal wall recurrence and was treated with pelvic radiation. She was still alive with no evidence of disease at the time of writing. Adjuvant RT was not given following her initial surgery and her GOG RS was 82 (intermediate RS).

In the study group (1997 to 1999), there was no recurrence or death from disease reported in the surgery-only group. A total of 2 (3.6%) recurrences were reported. One patient was from the modified field RT group who had a GOG RS

Table 3. Radiation-related Morbidity of Modified (Small) Field and Standard Field Radiotherapy Groups*

Morbidity	Standard field RT (n = 14)	Modified field RT (n = 13)
Grades 1 & 2		
Lymphoedema grade 1	3 (21%)	4 (31%)
Lymphoedema grade 2	1 (7%)	-
Rectum	5 (36%)	2 (15%)
Bladder	3 (21%)	3 (23%)
Non-specific abdominal symptoms	2 (14%)	1 (7%)
Grades 3 and 4	0	0

RT: radiotherapy

* Grading is based on the French-Italian glossary of complications,[22] except for lymphoedema which is based on the International Society of Lymphology.[23]

of 81. She developed liver metastasis after a disease-free interval of 9 months and died 6 months after diagnosis of the recurrence. The second patient who developed a relapse was from the standard field RT group, with a GOG RS of 153. The disease recurred at the pelvic sidewall after a disease-free interval of 7 months. She died 18 months after diagnosis of recurrence.

There was no significant difference in recurrence rates between the 2 study periods, nor was there any significant difference in the 3-year (the follow-up for 1997 to 1999 was <3 years) disease-free survival between the 2 groups (Fig. 1).

Figure 2 shows the disease-free survival curves for patients with a GOG RS of >120 (high risk) and treated with standard field RT. Figure 3 plots the disease-free survival curve for patients with a GOG RS of 40 to 120 (medium risk) and treated with modified field RT. There was a clear difference in disease-free survival between our patients with GOG score of >120 treated with standard field RT and that of a similar risk group in the GOG study that did not receive any adjuvant therapy.

Discussion

FIGO stage Ib cervical carcinoma may be treated either by radical surgery or RT. Both approaches have a 5-year survival rate ranging from 87% to 92%.[1,21] Radical hysterectomy has the advantages of preserving the gonadal and vaginal function, especially in young and sexually active women. Surgery allows detailed histopathological study of the cancer and status of the lymph nodes, which is the most important prognostic factor for survival. About 65% of our patients with FIGO stage Ib cervical carcinoma were treated with primary radical hysterectomy.

When the disease extends beyond the cervix or had metastasised to the lymph nodes, the employment of adjuvant RT – either alone or concurrently with chemotherapy – is less controversial to reduce the risk of pelvic relapse, although significant improvement in overall survival outcome is less clear.[5-7,9,11-13] In general, adjuvant RT is given for positive lymph node and surgical margins in about 30% of patients.[22]

Two-thirds of our patients had disease confined to the cervix and without lymph node metastases. Such patients had accounted for half of all early-stage cervical cancer recurrences.[23] Previously, the indications for pelvic RT were less precise at our centre, and in many other centres as well. They include large clinical tumour size, deep cervical stromal invasion and the presence of LVSI.[5,9,14] The decisions were often subjective and inconsistently applied in all cases.

Our study confirmed that the decision to employ adjuvant RT has not been consistent. In the surgery-only group, while the mean GOG RS was 22.3, 5 patients had scores of >40, which is at a higher risk of relapse compared with those having a score of <40 as shown by Delgado et al.[5] Similarly, while the mean GOG RS for patients who had adjuvant RT was higher at 66, the variance was large with 1 patient having a RS of <40 and 2 having a RS of >120.

We attempted to answer 3 questions. Firstly, did our patients who are at a high risk of having a relapse (GOG RS >120) derive the same survival benefits from having adjuvant pelvic RT as shown by the GOG study? Secondly, can we define a more precise and reliable indicator that can be consistently used to identify patients who can be safely left alone without having further pelvic RT? Finally, for patients deemed to be at a higher risk of pelvic relapse, can

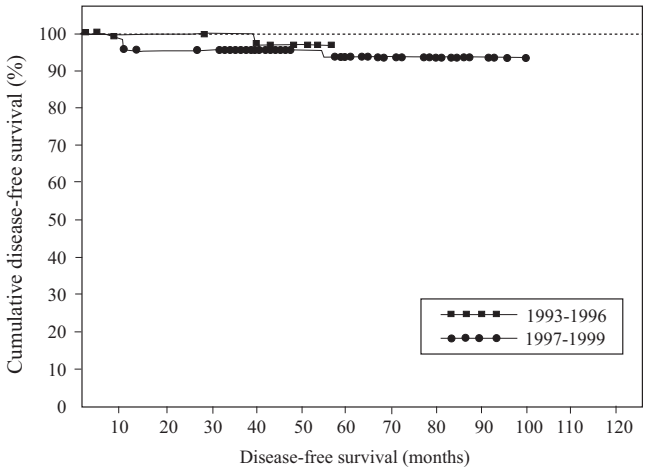

Fig. 1. Comparison of disease-free survival between 1993-1996 and 1997-1999.

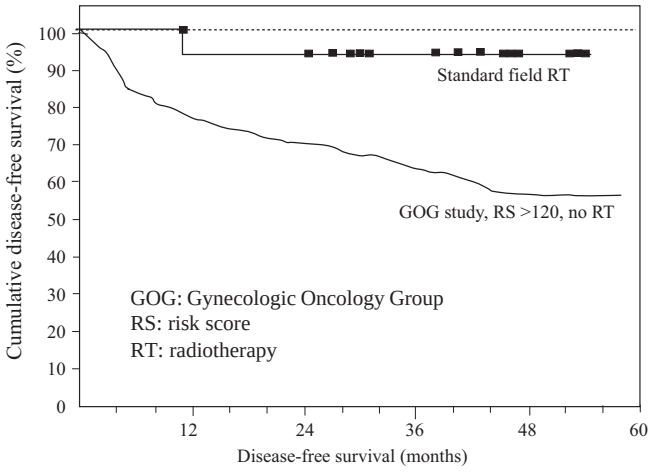

Fig. 2. Disease-free survival for stage Ib cervical carcinoma with a GOG RS >120 and treated with a standard field RT compared with that of the GOG study.

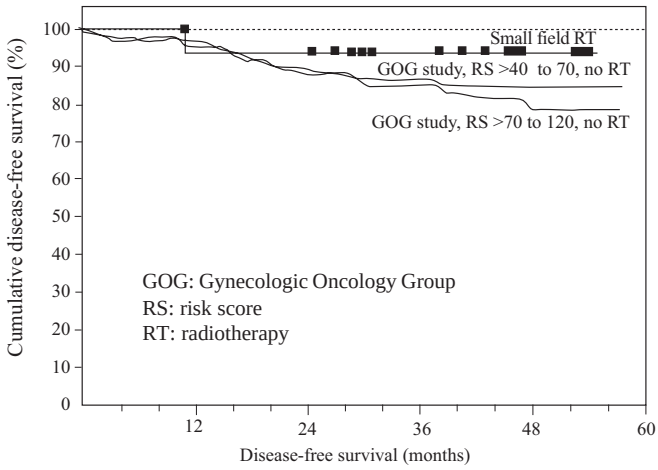

Fig. 3. Disease-free survival for stage Ib cervical carcinoma with a GOG RS of 40 to 120 (intermediate risk) treated with a modified (small) field RT compared with that of the GOG study.[5]

we tailor the field of the pelvic radiation without compromising the chance of cure based on current treatment regimen of a standard field pelvic RT?

First, similar to a previous study,[15] our results showed that postoperative adjuvant RT given to patients with a high GOG RS >120 significantly improved their 5-year recurrence rate and disease-free survival (Fig. 2). The risk of recurrence in a similar group of patients without adjuvant RT in the GOG study[5] was 41%. The follow-up period of our study was shorter and the risk of recurrence was 7.1%. Our result is similar to the study by Kridelka et al,[15] which had a recurrence rate of 5% in a cohort whose mean follow-up period was 32 months (range, 12 to 60 months). Similar results were also reported by other investigators,[9,14,15] including a randomised study[14] that showed that the risk of recurrence was significantly reduced by 44% in patients treated with RT ($P = 0.019$).

Secondly, in our treatment protocol, pelvic RT was withheld if the GOG RS <40. The mean RS for the 28 (51%) patients in the cohort treated from 1997 to 1999 was a low 9.4 (range, 1 to 35 months). None of the patients developed a pelvic recurrence after a mean follow-up period of 34.6 months (range, 5 to 50 months). If this result is maintained, the cut-off RS of 40 may be used to safely exclude a patient from undergoing adjuvant pelvic RT.

Thirdly, the role of adjuvant RT in the intermediate-risk group, defined as having a GOG RS of between 40 and 120, is more controversial. The risk of a recurrence within 5 years, without adjuvant treatment, was 20%.[5] In our study, it was 7.7% when a smaller modified field of pelvic RT was used. However, the GOG[5] study appeared to show an improvement. A definitive conclusion could not be inferred from a retrospective comparison of 2 different study cohorts with different sample sizes; our study cohort was much smaller. A prospective randomised controlled trial is necessary to define the exact role of adjuvant RT in intermediate-risk patients.

Two concerns were raised in this study. Firstly, are we over-prescribing RT when the indication is arbitrary? Secondly, more radiation-related morbidity may result from such treatment policy. We observed an increase in the use of postoperative pelvic RT for patients with FIGO stage Ib cervical cancer, confined to the cervix, from 25% in 1993-1996 to 50% in 1997-1999 (Table 1). Although the inherent differences between the 2 unmatched cohorts, in terms of patients' and tumour characteristics, may be contributive, there is genuine concern on our part as to whether the introduction of modified field RT for patients with an intermediate GOG RS of between 40 and 100 is largely responsible. The latter accounted for half of RT given in the 1997-1999 cohort. If it was withheld and given only to patients with a high GOG RS >120, the RT rate would have remained unchanged.

There is no ideal rate of adjuvant RT, but only an ideal treatment protocol that will result in the best survival outcome at the lowest possible cost of life-limiting morbidity. The mean rate of adjuvant RT in 5 previous studies was 18% (range, 9% to 35%).[24-26] These were standard field pelvic RT. The rate of grades 3 and 4 postoperative radiation-related morbidity, usually of the gastrointestinal and genitourinary systems, was reported by many studies to be as high as 10% to 12%.[14,15,27-29] The introduction of modified field RT is a relatively new attempt to find the right balance between treatment outcome and morbidity for patients with an intermediate GOG RS. Therefore, a prospective randomised controlled trial is essential to determine whether the use of such adjuvant RT for this group of patients is justifiable.

Regarding morbidity, we found that in both standard field and small field RT, none of our patients developed major morbidity (grades 3 and 4). Minor morbidity seemed to be slightly higher (36% versus 15%) in the standard field RT group. All minor radiation morbidity was self-limiting or required a short course of treatment. However, it is far too premature to conclude that modified field RT is safer than standard RT. A longer duration in follow-up is necessary to observe any differences in long-term morbidity.

As for relapse, 1 patient treated in 1993-1996 developed a pelvic recurrence and had a GOG RS (calculated retrospectively) of 81. In this case, a modified field pelvic RT would have been indicated based on current criteria. However, whether RT would have prevented the relapse is entirely speculative. Due to the small sample of the present study, a definite conclusion on survival outcome could not be made.

Conclusion

Our study indicated that postoperative adjuvant RT given in patients with a high GOG RS >120 significantly improved their 5-year recurrence rate and disease-free survival, compared with a similar group of patients who did not receive adjuvant RT in the GOG study.[5] Patients with a GOG RS <40 may be spared adjuvant pelvic RT. The current treatment protocol did not compromise the outcome of patients compared with the use of a less precise treatment protocol in the past.

This study enables us to further refine and define the role of adjuvant pelvic RT for FIGO stage Ib cervical carcinoma using precise risk profiles, especially for patients with intermediate GOG RS. Standardisation of treatment protocol will improve evidence-based decision-making, minimise inconsistency and reduce the risk of inappropriate treatment and potential litigation problems.

REFERENCES

1. Landoni F, Maneo A, Colombo A, Placa F, Milani R, Perego, et al. Randomised study of radical surgery versus radiotherapy for stage Ib-IIa cervical cancer. Lancet 1997;350:535-40.
2. Newton M. Radical hysterectomy or radiotherapy for stage I cervical cancer. A prospective comparison with 5 and 10 years follow-up. Am J Obstet Gynecol 1975;123:535-42.
3. Curtin JP, Hoskins WJ, Venkatraman ES, Almadrones L, Podratz KC, Long H, et al. Adjuvant chemotherapy versus chemotherapy plus pelvic irradiation for high-risk cervical cancer patients after radical hysterectomy and pelvic lymphadenectomy: a randomized phase III trial. Gynecol Oncol 1996;61:3-10.
4. Sevin BU, Lu Y, Bloch DA, Nadji M, Koechli OR, Averette HE. Surgically defined prognostic parameters in patients with early cervical carcinoma. A multivariate survival tree analysis. Cancer 1996;78: 1438-46.
5. Delgado G, Bundy B, Zaino R, Sevin BU, Creasman WT, Major F. Prospective surgical-pathological study of disease-free interval in patients with stage Ib squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. Gynecol Oncol 1990;38:352-7.
6. Lai CH, Chang HC, Chang TC, Hsueh S, Tang SG. Prognostic factors and impacts of adjuvant therapy in early-stage cervical carcinoma with pelvic node metastases. Gynecol Oncol 1993;51:390-6.
7. Atkovar G, Uzel O, Ozsahin M, Koca S, Sahinler I, Okkan S, et al. Postoperative radiotherapy in carcinoma of the cervix: treatment results and prognostic factors. Radiother Oncol 1995;35:198-205.
8. Lin HH, Cheng WF, Chan KW, Chang DY, Chen CK, Huang SC. Risk factors for recurrence in patients with stage Ib, IIa and IIb cervical carcinoma after radical hysterectomy and postoperative pelvic irradiation. Obstet Gynecol 1996;88:274-9.
9. Schorge JO, Molpus KL, Koelliker D, Nikrui N, Goodman A, Fuller AF Jr. Stage Ib and IIa cervical cancer with negative lymph nodes: the role of adjuvant radiotherapy after radical hysterectomy. Gynecol Oncol 1997;66:31-5.
10. Hart K, Han I, Deppe G, Malviya V, Malone J Jr, Christensen C, et al. Postoperative radiation for cervical cancer with pathologic risk factors. Int J Radiat Oncol Biol Phys 1997;37:833-8.
11. Tsai CS, Lai CH, Wang CC, Chang JT, Chang TC, Tseng CJ, et al .The prognostic factors for patients with early cervical cancer treated by radical hysterectomy and postoperative radiotherapy. Gynecol Oncol 1999;75:328-33.
12. Kim SM, Choi HS, Byun JS. Overall 5-year survival rate and prognostic factors in patients with stage Ib and IIa cervical cancer treated by radical hysterectomy and pelvic lymph node dissection. Int J Gynecol Cancer 2000;10:305-12.
13. Okada M, Kigawa J, Minagawa Y, Kanamori Y, Shimada M, Takahashi M, et al. Indication and efficacy of radiation therapy following radical surgery in patients with stage Ib to IIb cervical cancer. Gynecol Oncol 1998;70:61-4.
14. Sedlis A, Bundy BN, Rotman M, Lentz SS, Muderspach LI. Treatment of selected patients with stage Ib carcinoma of the cervix treated with radical hysterectomy and pelvic lymphadenectomy: pelvic radiation therapy versus no further therapy (a GOG study). Gynecol Oncol 1999;54:571-3
15. Kridelka FJ, Berg DO, Neuman M, Edwards LS, Robertson G, Grant PT, et al. Adjuvant small field pelvic radiation for patients with high risk, stage Ib lymph node-negative cervix carcinoma after radical hysterectomy and pelvic lymph node dissection. A pilot study. Cancer 1999;86: 2059-65.
16. Fiorica JV, Roberts WS, Greenberg H, Hoffman MS, LaPolla JP, Cavanagh D. Morbidity and survival patterns in patients after radical hysterectomy and postoperative adjuvant pelvic radiotherapy. Gynecol Oncol 1990;36:343-7.
17. Barter JF, Soong SJ, Shingleton HM, Hatch KD, Orr JW Jr. Complications of combined radical hysterectomy – postoperative radiation therapy in women with early stage cervical cancer. Gynecol Oncol 1989;32:292-6.
18. Piver MS, Rutledge F, Smith JP. Five classes of extended hysterectomy for women with cervical cancer. Obstet Gynecol 1974;44:265-72.
19. Chassagne D, Sismondi P, Horiot JC, Sinistrero G, Bey P, Zola P, et al. A glossary for reporting complications of treatment in gynecological cancers. Radiother Oncol 1993;26:195-202.
20. Kaplan EL, Meier P. Nonparametric estimation from incomplete observation. J Am Stat Assoc 1958;53:457-81.
21. International Society of Lymphology. The diagnosis and treatment of peripheral lymphedema. Consensus document of the International Society of Lymphology Executive Committee. Lymphology 1995;28:113-7.
22. Averette HE, Method MV, Sevin BU, Penalver MA. Radical abdominal hysterectomy in the primary management of invasive cervical cancer. In: Rubin SC, Hoskins WJ, editors. Cervical Cancer and Preinvasive Neoplasia. Philadelphia: Lippincott-Raven Publishers, 1996:189-206.
23. Samlal RAK, van der Velden J, Ketting BW, Gonzales D, Kate FJW, Harts AAM, et al. Disease free interval and recurrence pattern after the Okabayashi variant of Wertheim's radical hysterectomy for stage Ib and IIa cervical carcinoma. Int J Gynecol Cancer 1996;6:120.
24. Burke TW, Hoskins WJ, Heller PB, Bibro MC, Weiser EB, Park RC. Prognostic factors associated with radical hysterectomy failure. Gynecol Oncol 1987;26:153-9.
25. Soisson AP, Soper JT, Clarke-Pearson DL, Berchuck A, Montana G, Creasman WT. Adjuvant radiotherapy following radical hysterectomy for patients with stage Ib and IIa cervical cancer. Gynecol Oncol 1990;37:390-5.
26. Larson DM, Stringer CA, Copeland LJ, Gershenson DM, Malone JM Jr, Rutledge FN. Stage Ib cervical carcinoma treated with radical hysterectomy and pelvic lymphadenectomy. role of adjuvant radiotherapy. Obstet Gynecol 1987;69:378-81.
27. Rettenmaier MA, Casanova DM, Micha JP, Moran MF, Ramsanghani NS, Syed NA, et al. Radical hysterectomy and tailored postoperative radiation therapy in the management of bulky stage Ib cervical cancer. Cancer 1989;63:2220-3.
28. Monk BJ, Cha DS, Walker JL, Burger RA, Ramsinghani NS, Manetta A, et al. Extent of disease as an indication for pelvic radiation following radical hysterectomy and bilateral pelvic lymph node dissection in the treatment of stage Ib and IIa cervical carcinoma. Gynecol Oncol 1994;54: 4-9.
29. Kjorstad KE, Martimbeau PW, Iversen T. Stage Ib carcinoma of the cervix, the Norwegian Radium Hospital: results and complications. III. Urinary and gastrointestinal complications. Gynecol Oncol 1983;15: 42-7.