Risk for Radical Hysterectomy Failure

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Abstract

During the period from July 1983 to December 1996, 685 patients who underwent radical hysterectomy as their primary treatment for cervical cancer and had optimal follow-up for at least three years were analyzed. Fifty seven patients (8.3%) had pelvic nodes metastasis and received postoperative whole pelvic radiation. Tumor recurrence was noted in 97 cases (14.2%). Nodal metastasis is the most significant prognostic factor for tumor recurrence. Patients with nodal metastasis had 42.1 per cent risk of recurrence compared to 11.6 per cent in those without nodal metastasis. Furthermore; risk of recurrence significantly increased if more than 1 node was involved. Other factors associated with a significantly higher risk of recurrence in multivariate analysis were tumor histology and clinical stage. Patients with nonsquamous cell carcinoma and clinical stage IIa had disease recurrence in 24.4 per cent and 30.3 per cent compared to only 11.7 per cent in squamous and 13.3 per cent in stage Ib. Tumor grade is the significant prognostic factor only in adenocarcinoma cell type but not in squamous cell type.

Key word : Cervical Cancer, Radical Hysterectomy, Recurrence

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Patients with International Federation of Gynecology and Obstetrics (FIGO) stage Ib and IIa cervical cancer can be treated with either radical hysterectomy with pelvic nodes dissection or radiotherapy with an equal survival rate[1-3]. The choice of surgery or radiation for the treatment has generally been upon many factors such as age, medical status, patients' preference, experience and preference of the gynecologist and availability of facilities. With advanced surgical techniques; operative

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morbidity and mortality in radical pelvic surgery has been reduced. As a result, radical hysterectomy with pelvic nodes dissection has become one of the favored treatment modalities for stage Ib and IIa cervical cancer with approximately 80-90 per cent 5-year survival[3-6]. However, 10-20 per cent of the patients will develop recurrent disease[4,5,7-11] leading to death in more than 85 per cent of the recurrent cases[4,12].

The purpose of this study was to identify patients with early stage cervical cancer undergoing radical hysterectomy and pelvic nodes dissection who had high risk of tumor recurrence and were, therefore, potential candidates for adjuvant or alternative therapy.

PATIENTS AND METHOD

From July 1983 to December 1996, 855 patients with Stage Ib and IIa cervical cancer underwent radical hysterectomy with pelvic lymphadenectomy as their primary treatment at Maharaj Nakorn Chiang Mai Hospital. Medical records and pathology reports of these patients were retrospectively reviewed.

All patients were staged according to FIGO staging system at the time of clinical examination. The standard surveillance program after surgery included clinical history and physical examination every 3-4 months during the first 2 years and every 6 months during the third to fifth year. After 5 years of uncomplicated follow-up, the patient was seen annually.

Ninety-seven patients who developed recurrence were the target population of this study. Evidence of recurrence was confirmed by biopsy if possible. Chest X-ray, and computed tomography of the pelvis and abdomen were also used to determine the extent of disease. Seventy-two (74.2%) recurrences were confined only in the pelvis while twenty five (25.8%) were with distant metastasis. The median time from surgery to tumor recurrence was 1.4 years with the range of 1 month to 8.75 years. In 38 patients (39.2%), disease recurred within 1 year; in 62 (63.9%) within 2 years, in 81 (83.5%) within 3 years and 91 (93.8%) within 5 years.

Various factors such as patients' age, clinical stage, characteristic of the tumors, tumor histology, tumor size, presence of nodal metastasis and presence of parametrial involvement were analyzed for possible association with tumor recurrence compared to the control group (588 cases) who had no recurrence with optimal follow-up for at least 3 years, (median follow-up of 5.4 years (range 3-15.8 years)). Others who had no recurrence with less than 3-year- follow-up period (170 cases) were excluded. Statistical evaluation included Chi-squares or Fisher's exact test where applicable. Variables found to be significant in a univariate analysis were put into a multivariate stepwise logistic regression analysis using the SPSS statistical analysis software package. A probability value of less than 0.05 was considered to be statistically significant.

RESULTS

The six hundred and eighty five study patients had a median age of 39 years (range 21-70 years). The median age in the recurrent group was 38 years (range 21-67 years) which was not significantly different from 40 years (range 22-70 years) in the nonrecurrence group. (p= 0.446) Six hundred and fifty two (95.2%) were in stage Ib while 33 (4.8%) were in stage IIa. The size of the tumor ranged from occult lesion to 7 cm. Three hundred and twenty four had ulceroinfiltrative lesions while 209 had exophytic lesions. The most common histologic type was squamous cell carcinoma in 554 cases (80.9%; large cell keratinized 86, large cell nonkeratinized 218, small cell 195, not defined 55). Adenocarcinoma was diagnosed in 106 cases (15.5%; well differentiated 79, moderately differentiated 11, poorly differentiated 9, not defined 7). Adenosquamous, neuroendocrine and undifferentiated carcinoma were found in 11,13 and 1 case(s), respectively.

Fifty-seven patients had lymph nodes exhibiting metastasis. Eleven with parametrial invasion (9 also had nodal involvement while the other two had only parametrial involvement). The median number of involved node was 2 nodes with the range of 1-53 nodes, 20 patients had only single node metastasis. Patients with nodal and/or parametrial involvement were recommended to undergo further postoperative whole pelvic radiation. All but one had adjuvant pelvic radiotherapy for at least 5,000 cGy.

The influence of patients' age, clinical stage, characteristics of the tumor, tumor histology, tumor size, nodal involvement and parametrial involvement on the tumor recurrence were examined for possible association. By univariate analysis, all these variables except for patients' age and parametrial involvement are identified as significant

Table 1. Tumor recurrence in relation to patients' age, clinical stage, tumor characteristics, tumor histology, tumor size, nodal status and parametrial invasion.

	Number of patients	Recurrence		p value	Odd ratio	95% CI
		No	%			
Patients' age				0.193	0.6	0.3-1.3
≤ 30 years	49	10	20.4			
> 30 years	636	87	13.7			
Clinical stage				0.017	2.8	1.3-6.1
Ib	652	87	13.3			
IIa	33	10	30.3			
Tumor characteristics				0.011	1.8	1.1-2.8
Ulceroinfiltrative	324	44	13.6			
Exophytic	209	46	22.0			
Tumor histology				<0.0001	2.4	1.5-3.9
Squamous	554	65	11.7			
Nonsquamous	131	32	24.4			
Tumor size				<0.0001	2.9	1.8-4.7
≤ 4 cm	543	62	11.4			
> 4 cm	128	35	27.3			
Nodal status				<0.0001	5.5	3.1-9.9
Negative	628	73	11.6			
Positive	57	24	42.1			
Parametrial invasion				0.057	3.6	1.0-12.4
No parametrial invasion	674	93	13.8			
Parametrial invasion	11	4	36.4			
Total	685	97	14.2			

14 cases had no data available for tumor size
152 cases had occult lesion or undetermined tumor characteristics

Table 2. Result of multivariate analysis of tumor recurrence in relation to clinical stage, tumor characteristics, tumor histology, tumor size, nodal status and parametrial invasion.

Variables	Coefficient	SE	p-value
Clinical stage (Ib/IIa)	0.9913	0.4423	0.0250
Tumor characteristics (Ulceroinfiltrative/Exophytic)	0.4770	0.2529	0.0593
Tumor histology (Squamous/Nonsquamous)	0.1209	0.0395	0.0022
Tumor size (≤ 4 cm / > 4 cm)	-0.1501	0.1407	0.2859
Nodal status (negative/ positive)	1.5720	0.3545	< 0.00001
Parametrial invasion (not involved/ involved)	-0.1534	0.7750	0.8431

prognostic factors for tumor recurrence. (Table 1) However, multivariate analysis of these factors shows that only pelvic node metastasis, tumor histology and clinical stage remain significant. (Table 2)

From this analysis, pelvic nodes metastasis seems to be the most significant prognostic factor. Patients with nodal metastasis had 5.5 times (95% CI of 3.1-9.9) risk of recurrence compared to those without nodal metastasis. Furthermore, the number of involved nodes was also the significant factor. Patients with only single node involvement had 20.0 per cent risk of recurrence while those with multiple nodal involvement had 55.6 per cent risk of recurrence. (p=0.010; odd ratio=5.0, 95% CI=1.4-17.9)

Tumor histology was the second most important prognostic factor for tumor recurrence. Patients with nonsquamous cell carcinoma had a 2.4 times higher risk of recurrence compared to squa-

mous cell carcinoma. (Table 1) In squamous cell carcinoma, different histologic types had no significant influence on tumor recurrence, patients with large cell keratinized, large cell non-keratinized and small cell had 7.0 per cent, 11.9 per cent and 14.9 per cent risk of recurrence (p=0.1) However, in adenocarcinoma cell type which had a 21.7 per cent risk of recurrence, degree of differentiation was one of the significant risks of recurrence. Patients with moderate or poorly differentiated had a 55.0 per cent risk of recurrence compared to 13.9 per cent in well differentiated group. (odd ratio of 7.6, 95% CI = 2.5 - 22.4, p value < 0.0001). Adenosquamous cell carcinoma and neuroendocrine carcinoma also demonstrated high risk of recurrence ; 18.2 per cent and 46.2 per cent respectively.

DISCUSSION

During the fourteen-year study period, a large number of patients with FIGO stage Ib and IIa cervical cancer underwent radical hysterectomy and pelvic nodes dissection at Maharaj Nakorn Chiang Mai Hospital. The risk of recurrence in our series was 14.2 per cent. This compared favorably to 10-20 per cent in other reports[4,5,7-11]. Since recurrence was concordant with death in more than 85 per cent of such patients[4,12], the aim of this study was to concentrate on risk factors as related to tumor recurrence. In this study, the control group was patients who had no recurrence with a follow-up period of at least 3 years. We used the cut off point at three years because more than eighty per cent of our patients recurred within 3 years, this is somewhat different from other reports with about 80 per cent of their patients recurring within 2 years[7,9,10].

In the present study, pelvic node metastasis was the most important prognostic factor associated with an increased risk of recurrence (42.1%). This was consistent with the findings of Zaino et al[13]. In addition, we also found that there was a higher chance of recurrence if more than 1 node was involved. Yeh et al[14] also reported that survival tended to decrease among patients with multiple positive nodes compared to those with one node metastasis.

Parametrial involvement, one of the important risk factors in the study of Finan[15], lost its borderline significant risk of recurrence in multivariate analysis which reflected that this factor was a dependent factor since 9 in 11 patients with parametrial invasion also had nodal metastasis.

Considering tumor histology, there was some conflicting prognosis of cervical cancer. Some have reported that adenocarcinoma had a higher risk of recurrence than their squamous counterpart[7-10]. Others have suggested that these two histological types did not differ in their prognosis[16]. Chen et al[17] also reported that in stage I and II cervical cancer, a higher survival rate for squamous cell carcinoma compared to adenocarcinoma was found only in cases that underwent radiotherapy but not cases that underwent surgery[18]. However, in our study, we clearly showed that cervical cancer patients with adenocarcinoma treated by surgery had a poorer prognosis than those with squamous cell carcinoma because of a higher risk of recurrence confirmed by both univariate and multivariate analysis.

Concerning degree of differentiation, there was also some controversy. Some reports could not demonstrate significant correlation between the degree of tumor differentiation and survival[19,20], but others have drawn the opposite conclusion[4,6]. Our study showed that tumor grade had a significant correlation with tumor recurrence only in adenocaricnoma but not in squamous cell carcinoma. Zaino et al[13] also reported that histologic grading has no prognostic significance for squamous cell carcinoma.

Regarding tumor stages, in this study, there was significant difference in the recurrent rate in stage IIa (30.3%) and Ib (13.3%). The study of Fuller et al[4] also showed that patients with stage IIa had a significantly lower survival rate than stage Ib (72% *versus* 86%). In contrast, the study of Yeh et al [14] demonstrated that there was no difference in survival or pelvic control rates between these two stages.

The association of the characteristics of the tumor and prognosis of cervical cancer has not been claimed often in other papers[4,6,8]. The reason may be that while some lesions are easy to distinguish, some lesions are hard to determine whether they are exophytic or ulceroinfiltrative lesions because there is no clear cut point to separate these lesions from each other. In our study, 153 cases (22.3%) had no data as to whether the lesion was exophytic or ulceroinfiltrative because some were occult lesions and some were lesions which could

not be determined. However, exophytic lesions seemed to have a higher, though not significant, risk of recurrence than ulceroinfiltrative lesions in this multivariate analysis (p=0.0593).

Size of tumor which is one of the significant prognostic factors in univariate analysis lost its significant association with tumor recurrrence in multivariate analysis. The reason should be that tumor size is not an independent prognostic factor. Higher risk of recurrence in large tumors in univariate analysis may be from an increased incidence of nodal metastasis in bulky tumors.

Conflicting results regarding the effect of age on prognosis in cervical cancer have been reported in the literature. Some reported that cervical cancer is more aggressive in young women[21, 22]. On the other hand, Alvarez et al[23] reported that youth conferred a survival advantage. Others, including our study, indicated that carcinoma of the cervix had the same prognosis in younger and older patients[6,24-26].

In summary, it appears that presence of nodal metastasis, clinical stage and tumor histology per se, are the significant prognostic parameters for tumor recurrence in early stage cervical cancer patients undergoing radical hysterectomy and pelvic node dissection. Since patients who developed recurrence had little chance of cure. The increased survival in cervical cancer is most likely to be achieved by reducing the incidence of recurrent disease. This study provided a mean of selecting patients at risk of recurrence who might benefit from alternative or adjuvant therapy. However, what therapy is appropriate and yield the best result needs to be studied further perhaps in a randomized controlled manner.

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REFERENCES

1. Roddick JR Jr, Greenlaw RH. Treatment of cervical cancer : a randomized study of operation and radiation. Am J Obstet Gynecol 1971; 109: 754-64.
2. Newton M. Radical hysterectomy or radiotherapy for stage I cervical cancer. A prospective comparison with five and ten year follow-up. Am J Obstet Gynecol 1975; 123: 535-43.
3. Morley GW, Seski JC. Radical pelvic surgery *versus* radiation therapy for stage I carcinoma of the cervix (exclusive of microinvasive) Am J Obstet Gynecol 1976; 126: 785-98.
4. Fuller AF Jr, Elliott N, Kosloff C, Hoskins WJ, Lewis JL Jr. Determinants of increased risk for recurrence in patients undergoing radical hysterectomy for stage IB and IIA carcinoma of the cervix. Gynecol Oncol 1989; 33: 34-9.
5. Martimbeau PW, Kjorstad KE, Kolstad P. Stage Ib carcinoma of the cervix, The Norwegian Radium Hospital, 1968-1970 : results of treatment and major complications. IE. Lymphedema. Am J Obstet Gynecol 1978; 131: 389-95.
6. Hopkins MP, Morley GW. Stage IB squamous cell cancer of the cervix : clinicopathologic features related to survival. Am J Obstet Gynecol 1991; 164: 1520-9.
7. Burke TW, Hoskins WJ, Heller PB, Shen MC, Weiser EB, Park RC. Clinical patterns of tumor recurrence after radical hysterectomy in stage IB cervical carcinoma. Obstet Gynecol 1987; 69: 382-5.
8. 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.
9. Krebs HB, Helmkamp BF, Sevin BY, et al. Recurrent cancer of the cervix following radical hysterectomy and pelvic node dissection. Obstet Gynecol 1982; 59: 422-7.
10. Larson DM, Copeland LJ, Stringer CA, Gershenson DM, Malone JM Jr, Edwards CL. Recurrent cervical carcinoma after radical hysterectomy. Gynecol Oncol 1988; 30: 381-7.
11. Webb MJ, Symmonds RE. Site of recurrence of cervical cancer after radical hysterectomy. Am J Obstet Gynecol 1980; 138: 813-7.

12. Barber HRK, O'neil WH. Recurrent cervical cancer after treatment by a primary surgical program. Obstet Gynecol 1971; 37: 165-72.
13. Zaino RJ, Ward S, Delgado G, et al. Histopathologic predictors of the behavior of surgically treated stage IB squamous cell carcinoma of the cervix. A Gynecologic Oncology Group Study. Cancer 1992; 69: 1750-8.
14. Yeh A, Leung SW, Wang C, Chen H. Postoperative radiotherapy in early stage carcinoma of the uterine cervix: treatment results and prognostic factors. Gynecol Oncol 1999; 72: 10-5.
15. Finan MA, De Cesare S, Fiorica JV. Radical hysterectomy for stage IB1 *vs* IB2 carcinoma of the cervix : does the new staging system predict morbidity and survival ? Gynecol Oncol 1996; 62: 139-47.
16. Shingleton HM, Bell MC, Fremgen A, et al. Is there really a difference in survival of women with squamous cell carcinoma, adenocarcinoma, and adenosquamous cell carcinoma of the cervix ? Cancer 1995; 76: 1948-55.
17. Chen R, Lin Y, Chen C, Huang S, Chow S, Hsieh C. Influence of histologic type and age on survival rates for invasive cervical carcinoma in Taiwan. Gynecol Oncol 1999; 73: 184-90.
18. Oka K, Nakano T, Hoshi T. Analysis of response to radiation therapy of patients with cervical adenocarcinoma compared with squamous cell carcinoma. MIB-I and PC10 labeling indices. Cancer 1996; 77: 2280-5.
19. Goellner JR. Carcinoma of the cervix : clinicopathologic correlation of 196 cases. Am J Clin Pathol 1976; 66: 775-85.
20. Crissman JD, Budhraja M, Aron BS, Cummings G. Histopathologic prognostic factors in stage II and III squamous cell carcinoma of the uterine cervix: an evaluationof 91 patients treated primarily with radiation therapy. Int J Gynecol Pathol 1987; 6: 97-103.
21. Dattoli MJ, Gretz HF III, Beller U, et al. Analysis of multiple prognostic factors in patients with stage IB cervical cancer : age as a major determinant. Int J Radiat Oncol Biol Phys 1989; 17: 41-7.
22. Rutledge FN, Mitchell MF, Munsell M, Bass S, McGuffee V, Atkinson EN. Youth as a prognostic factor in carcinoma of the cervix: a matched analysis. Gynecol Oncol 1992; 44: 123-30.
23. Alvarez RD, Soong SJ, Kinney WK, et al. Identification of prognostic factors and risk groups in patients found to have nodal metastasis at the time of radical hysterectomy for early stage squamous carcinoma of the cervix. Gynecol Oncol 1989; 35: 130-5.
24. Smales E, Perry CM, Ashby MA, Baker JW. The influence of age on the prognosis in carcinoma of the cervix. Br J Obstet Gynaecol 1987; 94: 784-7.
25. Prempree T, Patanaphan V, Sewchand W, Scott M. The influence of patients' age and tumor grade on the prognosis of carcinoma of the cervix. Cancer 1983; 51: 1764-71.
26. Stanhope CR, Smith JP, Wharton JT, et al. The effect of age on survival. Gynecol Oncol 1980; 10: 188-93.

ปัจจัยเสี่ยงของการกลับเป็นซ้ำในผู้ป่วยมะเร็งปากมดลูกที่รักษาด้วยการผ่าตัดมดลูกแบบตอนราก

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ระหว่างเดือนกรกฎาคม 2526 ถึง ธันวาคม 2539 มีผู้ป่วยมะเร็งปากมดลูกที่ได้รับการผ่าตัดมดลูกแบบตอนราก (radical hysterectomy) และมาติดตามการรักษาอย่างน้อย 3 ปี 685 ราย ผู้ป่วย 57 ราย (8.3%) พบว่ามะเร็งได้กระจายไปยังต่อมน้ำเหลืองในอุ้งเชิงกรานแล้ว ผู้ป่วยเหล่านี้ได้รับการรักษาต่อด้วยการฉายแสง ผู้ป่วย 97 ราย (14.2%) มีการกลับเป็นซ้ำของโรค การกระจายของมะเร็งไปต่อมน้ำเหลืองเป็นปัจจัยเสี่ยงที่สำคัญที่สุดของการกลับเป็นซ้ำของโรค ผู้ป่วยที่มะเร็งกระจายไปต่อมน้ำเหลืองแล้วมีการกลับเป็นซ้ำ 42.1% เทียบกับ 11.6% ในผู้ป่วยที่มะเร็งยังไม่กระจายไปต่อมน้ำเหลือง นอกจากนี้ผู้ป่วยที่มะเร็งกระจายไปต่อมน้ำเหลืองมากกว่า 1 ต่อมจะยิ่งมีอัตราการกลับเป็นซ้ำสูงขึ้น ปัจจัยอื่นที่สัมพันธ์กับการกลับเป็นซ้ำของมะเร็งอย่างมีนัยสำคัญทางสถิติ ได้แก่ ชนิดของมะเร็ง และระยะของโรค โดยพบว่ามะเร็งชนิด non-squamous และมะเร็งในระยะ IIa มีการกลับเป็นซ้ำ 24.4% และ 30.3% ตามลำดับ เปรียบเทียบกับ 11.7% ในมะเร็งชนิด squamous และ 13.3% ในมะเร็งระยะ IB สำหรับ tumor grade นั้นสัมพันธ์กับการกลับเป็นซ้ำอย่างมีนัยสำคัญทางสถิติเฉพาะในมะเร็งชนิด adenocarcinoma แต่ไม่มีนัยสำคัญทางสถิติในมะเร็งชนิด squamous

คำสำคัญ : มะเร็งปากมดลูก, การผ่าตัดมดลูกแบบตอนราก, การกลับเป็นซ้ำ

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