Radiation Therapy Results of Invasive Cervical Carcinoma Found After Inappropriate Hysterectomy

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= Abstract =

Purpose : Hysterectomy without lymph node dissection was considered an inadequate treatment method for invasive uterine cervix cancer. Usually the procedure was performed inadvertently on patients who were thought to have benign or premalignant conditions preoperatively. We analysed radiotherapy results of such patients to evaluate survival rates, failure patterns and prognostic factors according to various conditions.

Materials and Methods : Sixty one patients undergoing hysterectomy in the presence of invasive cervical carcinoma were reviewed retrospectively. Preoperative diagnosis were carcinoma in situ (38 cases), severe dysplasia (2), myoma (6), uterine bleeding (4), uterine prolapse (2), and early invasive cervix cancer (10) (One patient had myoma and carcinoma in situ coincidently). Patients received postoperative megavoltage radiotherapy from August 1985 to December 1993, and minimum follow-up period was 24 months. Eight patients received ICR only, 6 patients ICR and external radiation, and 47 patients received external radiation therapy only.

Results : Overall 5-year survival rate and relapse-free survival rate were 83.8%, 86.9% respectively. For patients with retrospective stage IA, IB, IIB (gross residual after surgery), and vaginal cuff recurrence were 90.9%, 88.8%, 38.4%, and 100% respectively. There were 8 cases of treatment failure, most of them (5/8) were in patients with gross residual disease, other patients were full thickness involvement of cervix wall (2/8) except one. Patients with early vaginal cuff recurrence and microinvasive cervical cancer (stage IA) had no treatment related failure. Prognostic factors affecting survival by univariate analysis were status of residual disease, tumor histology and retrospective stage.

Conclusion : Adjuvant radiotherapy appeared to be effective treatment method for patients with presumed stage IA, IB and early local recurrent disease after inadvertent hysterectomy. Survivals for patients with gross disease remained after inappropriate hysterectomy was poor. So, early cancer detection and proper management with precise pretreatment staging is

necessary to avoid inadherent hysterectomy especially in the cases of gross residual disease.

Key Words : Cervical carcinoma, Inappropriate hysterectomy, Postoperative radiotherapy

INTRODUCTION

Screening and early detection of uterine cervical cancer has resulted in an increase in the relative incidence of early stage cancer. But, Papanicolaou smears have about 20% false negative rate in the best hands[1]. These facts suggest that gynecologist often found to have invasive cancer in the surgical specimen at the time of total (simple extrafascial) hysterectomy for other indications.

Total hysterectomy alone for the treatment of invasive cervix cancer results in a risk of recurrence as high as 60%[2]. Multiple early reviews reported poor survival after radiotherapy and advocated radical reoperation as the treatment of choice[3-5], and at some institution, the accepted practice is still to perform reoperation to complete their treatment[6, 7]. With the development of radiation therapy, improved survival rates were reported from numerous institutions usually in patients with no gross residual disease after hysterectomy[8-12]. Patients confirmed with gross residual disease in the surgical specimen after inadequate surgery and postoperative radiotherapy have poor survival results than radical surgery or radical radiation therapy[12, 13].

There is little known prognostic factor except the status of gross disease after inadequate hysterectomy. We reviewed 61 cases of invasive cervical cancer after inappropriate surgery for various benign, premalignant conditions or early invasive cancers and analysed these data to quantitate survival, to identify significant prognostic factors, and to delineate the site of treatment failure.

MATERIALS AND METHODS

We reviewed the records of all patients with invasive cervical cancer treated postoperative radiation therapy at the Depatrment of Radiation Oncology, Soonchunhyang University Hospital and selected 61 patients performed with inadvertent surgery from September 1985 to December 1993.

The median age was 49 years (range, 27 to 70 years). Histopathology of uterine cervical malignancy consisted mostly of the squamous cell carcinoma type (57 patiens); there were four cases of adenocarcinoma (for the purpose of this analysis, one case of adenosquamous carcinoma was considered a subtype of adenocarcinoma). The mode of hysterectomy was mainly of the total abdominal hysterectomy (54 patients) or total vaginal hysterectomy procedure (7 patients), and the initial surgical procedure was performed at the Soonchunhyang University Hospital in 16 cases and elsewhere in 45 cases. In all of these patients, biopsy of the suspicious nodes was not performed.

Causes of inappropriate hysterectomy listed in Table 1. Most frequent cause was preoperative diagnosed as carcinoma in situ. Preoperative cervical sampling had not been performed in the patients undergoing emergency hysterectomy for 2 cases of uterine hemorrage. Ten patients had originally undergone total hysterectomy as intended treatment for a known early invasive cancer. This is not unusual method of operation in the provincial hospital in Korea and also, there has been a trend in recent years toward conservative management of

Table 1. Causes of Inappropriate Hysterectomy

preop. diagnosis	No. of patients	(%)
carcinoma in situ	38*	(62.3)
severe dysplasia	2	(3.3)
FIGO stage IA	7	(11.5)
FIGO stage IB	3	(4.9)
myoma	6*	(9.8)
uterine bleedings	4	(6.5)
uterine prolapse	2	(3.3)

* one patient had CIS and myoma coincidentally

Table 2. Histopathologic Findings

	No. of patients	(%)
Retrospective Stage		
IA	18	(29.5)
IB	33	(54.1)
IIB	7	(11.5)
recurrence	3	(4.9)
Histology		
squamous cell ca	57	(93.4)
adenocarcinoma	4*	(6.6)

* including one case of adenosquamous cell ca

Table 3. Radiation Treatment Plan

Retrospective	No. of patients	External RT	ICR
IA*	18	12	7
IB*	33	21	3
IIB*	7	7	1
Recurrence	3	3	3

* each group included one case of vaginal resection margin involvement and ICR treatment

many early invasive gynecologic cancers. There were three patients performed hysterectomy deliberately although preoperative stage were IB. One of them refused radical hysterectomy and blood transfusion due to religious belief (She was a Christian for the Seventh-Day Adventist Church), and gynecologist had to perform simple hysterectomy without transfusion during operation. The pathologic report represented no gross residual disease by good fortune and she is still alive without recurrence 5 years after surgery and radiotherapy. Another patient planned to undergo operation radically including lymph node dissection, she had total hysterectomy due to adjacent tissue invasion. She received postoperative radiotherapy but had local recurrence within one year, succumbed to cancer 3 months later. Ther other patient who had total hysterectomy in a community hospital for unknown causes, recurred locally (previous parametrial invasion site) within 2 years and expired.

Invasion of depth of all selected patients for this analysis was 3 mm or more as measured from the basement membrane and/or lymphatic vessel invasion in the hysterectomy specimen. It was possible to retrospectively assign a stage in all cases and patients referred for treatment at the time of recurrence were considered unstaged (Table 2). Retrospective staging according to FIGO criteria was accomplished on the basis of the pathologic report as well as the results of posthysterectomy evaluation including physical examination, computed tomograpy.

Radiotherapy started within 8 weeks after operation (55 patients), 3 patients received 2-3 cycles of chemotherapy and started radiotherapy 9-16 weeks after operation, 3 patients treated after pathologic confirmation of recurrence during follow up period. Principles of radiation therapy were as follows: External-beam irradiation of the pelvis, which included the vaginal cuff, was used in most of patients through the 4-MV X-ray linear accelerator with four field box technique. External radiation dosage were 45-50 Gy/ 5-6 weeks for retrospectively staged IA or IB patients, 45-50 Gy with 10 Gy boost dose/ 6-7 weeks for stage IIB patients. Some patients with stage Ia received only high dose rate remote afterloading intracavitary (IC) vaginal cuff irradiation between 30-40 Gy at 0.5cm from surface. Patients with vaginal resection margin involvement, recurrent cases or some of stage IA-IIB received external radiotherapy and additional vaginal cuff IC postoperative irradiation (Table 3).

Three of the patients were considered to be lost follow-up from 12 months to 20 months, others had a minimum follow-up period of 24 months. Diagnosis of treatment failures were based on strong suggestive evidence of disease on either clinical examination or biopsy or radiographic studies.

Survival rate and log rank test were carried out using SPSS to identify important prognostic factors of survival. To compare the risk of tumor related death with regard to the potential risk, univariate and stepwise multivariate Cox proportional hazard model were performed. Those dying of intercurrent disease were censored from the progression free survival estimates.

RESULTS
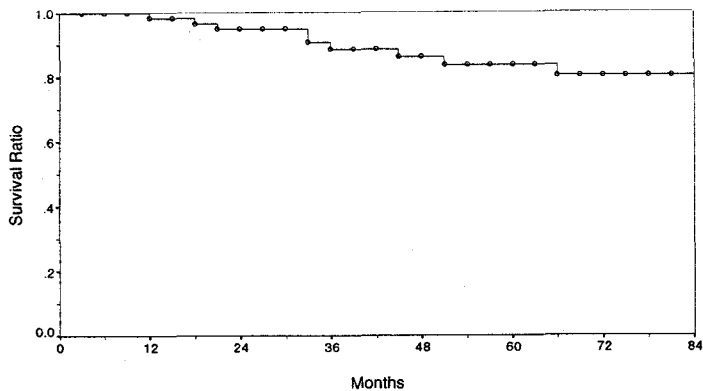
Fig. 1 shows the overall survivals for all of the

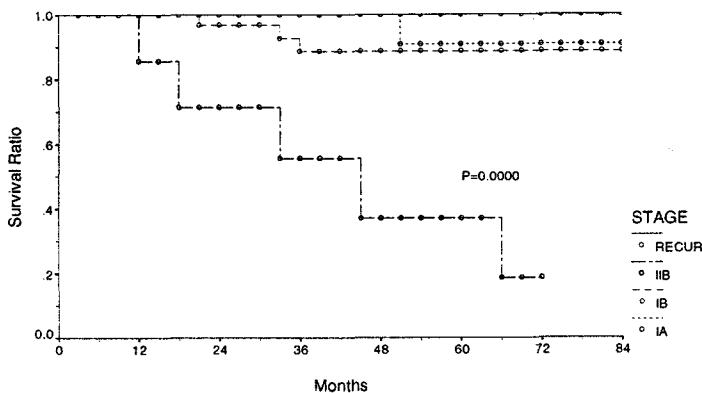Fig. 1. Overall survival rate of 61 patients.

Fig. 2. Overall survival by retrospective stage.

patients. Two and 5 year overall survival rates were 95.0%, 83.8%, respectively and relapse free 5 year survival rate was 86.9%. Fig. 2 demonstrated the overall survivals according to retrospective FIGO stage. Five year survival rates for stage IA, IB, IIB and recurrence were 90.9%, 88.8%, 38.4% and 100% respectively (p=0.0000). The 5 year survivals for patients with and without gross disease at the time of radiotherapy were 62.3%, 89.2%, respectively (Fig. 3). According to preoperative diagnosis, 5 year overall survival rates for benign disease, carcinoma in situ (including severe dysplasia), invasive cancer were 73.3%, 90.2%, and 67.5%, respectively (p= 0.0893)(Fig. 4). Five year survival rates by histology were 87.1% for squamous cell and 37.5% for

adenocarcinoma (p=0.0065).

There were 8 cases of treatment failure. Five of the 7 patients (71.4%) with presumed stage IIB succumbed to their disease. Disease recurrence developed in 3 patients in stage IB (8.8%), and the two of the three patients showed involvement of full thickness of uterine body in pathology, nearby stage II (There were 5 cases of full thickness involvement of uterine cervix wall confirmed in the pathologic specimen, so the failure rate of these patients was 40%). There were no recurrence in patients with stage IA or recurrent cases. One patient with stage IA with esophageal varix died from intercurrent disease (varix bleeding after 50 months of radiation treatment) although she was recurrence free at that
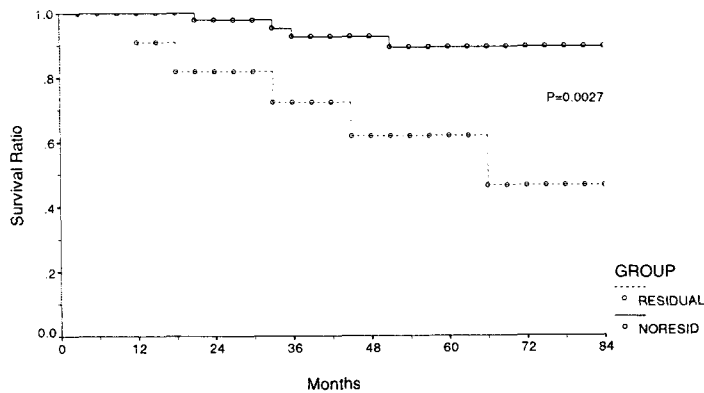
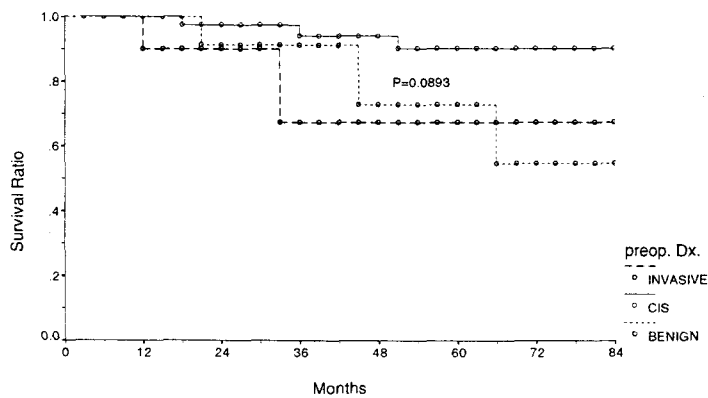Fig. 3. Overall survival for patients with and without gross disease.

Fig. 4. Overall survival according to preoperative diagnosis.

Table 4. Failure Patterns According to Retrospective Stage

Stage	No.	Local	DM*	Local+DM	Intercurrent dis.
IA	18	0	0	0	1
IB	33	1	2	0	0
IIB	7	3	1	1	0
Recur	3	0	0	0	0

* DM : distant metastasis

event. Three cases of vaginal recurrence occurred during regular follow up after hysterectomy. Their preoperative diagnosis were carcinoma in situ and pathologic report revealed early invasive cancer without resection margin involvement and they received no further therapy postoperatively. After

treatment of external radiotherapy and ICR, there was no treatment failure with more than 4 year duration.

Sites of recurrence are shown in Table 4. Locoregional failure occurred in only one of the 51 patients with no gross disease, whereas in patients with gross disease 4 (40%) locoregional failures occurred.

Since the information on some of our patients was obtained by correspondence, we could not exactly evaluate complication rate although some patients complained minor complication during or after radiotherapy, which was successfully treated with conservative management. None of the patients had major complication requiring medical manage-

Table 5. Prognostic Factors

Factors	Univariate	Multivariate
Retrospective stage	0.0000	0.1691*
Residual disease	0.0027	0.5793
Histology	0.0065	0.8566
Age	0.5606	0.8472
Time to referral	0.5194	0.9826
Causes of operation	0.0893	0.8226

Table 6. Survival According to Methods of Postop Treatment

Author	No. of patients	Type of treatment	5-year survival(%)
Jones and Jones	36	X*	42
Schmit	26	X	60 [16]**
Green and Morse	84	Reoperation	67
		Radiotherapy	30
Andras	118	Radiotherapy	89 [32]
Davy	72	Radiotherapy	77 [37]
Papavasilou	36	Radiotherapy	89
Roman	122	Radiotherapy	75 [39]
Kinney	27	Reoperation	82
This series	61	Radiotherapy	84 [38]

X* : No further treatment
[ ]** : Survival with gross residual

ment with admission or operative intervention.

The results of the univariate and multivariate Cox proportional hazard analysis, factor found to be significantly affecting survival rates were retrospective stage, status of gross disease at the time of radiation treatment referral, and tumor histology. On multivariate analysis, there were no factors emerging as significantly adverse to survival (Table 5).

DISCUSSION

Total vaginal or abdominal hysterectomy continues to be a frequently performed gynecologic procedure for various indications. Patients with carcinoma in situ, which may include those with severe dysplasia are best treated with a total hysterectomy with or without a small vaginal cuff[14]. Irradiation may be useful for the treatment of in situ carcinoma (and stage IA) particularly in patients with strong medical contraindications for surgery or when there is extension of the lesion to the vaginal wall or multiforcal carcinoma in situ both in the cervix and the

vagina[15].

The definition and treatment of microinvasive carcinoma of the cervix lacks uniformity. When the depth of penetrtion of the stroma by tumor is less than 3 mm, the incidence of lymph node metastasis is 1% or less, and a lymph node dissection or pelvic external beam irradiation is not warrented because the surgical morbidity and mortality rate for radical hysterectomy remains consistently higher than that for conservative hysterectomy[16-18]. With more extensive lesions of the stage IA, if there is any doubt as to whether the depth of stromal invasion extends beyond 3 mm or whether lymph-vascular space invasion by tumor cell is present, the patients should be treated by radical operation or radiotherapy. Tumor control with all treatment methods is close to 100%, with patients eventually dying of intercurrent disease[18, 19].

While the use of screening cervical cytology before performing a hysterectomy is considered to be the standard of care, many gynecologist may receive a pathology report indicating the presence of invasive cervix cancer after a total hysterectomy performed for benign indications or carcinoma in situ (and sometimes early invasive cancer less than 3 mm depth). Pathologic reports may represent microscopic invasive disease or surgically positive margins (microscopically or macroscopically).

Many studies reported poor results after total hysterectomy alone for invasive carcinoma of the cervix even when the disease is entirely limited to the uterine cervix. In 1943, Jones and Jones reported a 41.6% 5 year survival rate in 36 patients with early stage I cervical carcinoma who had been treated with hysterectomy alone[2]. Schmit, in 1951 reported that 5 year survival rate was 60% when a lesion was confined to the cervix and only 16% with involvement of surgical margin[20].

As a rule, total hysterectomy is not curative for the management of early invasive carcinoma because the paravaginal and paracervical soft tissue including the upper vagina and pelvic lymph nodes are not removed. For those reasons supplemental treatment is usually advocated. The mainstay of additional therapy in patients with cervical cancer

after inadvertent hysterectomy had been radiotherapy or radical reoperation. Five year survival rates after postoperative radiotherapy in patients with invasive cervical cancer who had a simple hysterectomy that apparently clear the disease ranged from 71 to 90%[9, 10, 12, 13, 21], except one poor survival data with a 5 year survival rate of 30% in all patients receiving curative radiotherapy at Pondville State Cancer Center from 1940 to 1960, which is not clear how soon curative rdiotherapy was begun and presumably the energy of radiation equipment was orthovoltage.

For similar patients, Orr et al[7] reported 3 year survival rate 96% after radical parametrectomy and pelvic lymphadenectomy. They recommended a radical reoperation should be considered a safe and efficacious alternative to pelvic radiation for patients who are deemed to require additional therapy avoiding many risks of radiation therapy effects such as loss of ovarian function, vaginal distortion, sexual dysfunction, bowel or urinary complication or carcinogenesis.

Kinney et al[6] reported an 82% 5-year survival rate comparable with that reported for similar patients treated with irradiation. Current data, a 5 year survival rate of 83% is also comparable with other reporta after radiation. At present most institutions have preferred to treat women in this situation with radiotherapy, despite the fact that these women are frequently young and would be considered candidates for radical surgery if they had presented initially with known stage IA or IB cervix cancer. The reasons for preferred radiation treatment than radical reoperation is probably a posthysterectomy radical parametrectomy would seem to be technically more difficult than radical hysterectomy.

Survival of patients with gross disease when posthysterectomy treatment commences has been uniformly poor. Reported survival rates for patients with gross disease receiving radiotherapy ranged from 23 to 43%[8, 12, 21]. Our survival data with gross disease is 62.3%, superior to other series, but excluding 3 cases of recurrence (all of them were cured), the 5 year survival rate of pure gross disease (stage IIB) is 38.4%, dismal result similar to

other series. In addition to poor results of gross disease, patients with full thickness involvement of uterine cervix wall revealed also risky (failure rate 40%).

Generally, 5-year survival rate for patients with FIGO stage IIB cervical cancer treated with radical radiotherapy is in the range of 60–80%, better results than inappropriate surgery and addition of radiation therapy. Many factors may be considered as the causes, such as the time elapsed between surgery and radiation, postoperative fibrosis that may render the region avascular (and hypoxic state), and the absence of the uterus precludes optimal dosimetry especially during intracavitary radiation. Another methods to control gross disease after hysterectomy is pelvic exenteration, a 39.4% survival in the study of Barber et al[4].

With a megavoltage radiation treatment, we obtained 5 year survival rates about 90% for patients with no gross disease and 38.4% for the seven patients with gross residual disease present after surgery. There were 8 cases of treatment failure, all of them eventually succumbed. The sites of recurrence were the pelvis and distant location, more frequently in the pelvic failure in gross residual disease suggesting lack of local control plays a major role in these patients.

Many authors recommend that early stage disease may be treated with intracavitary radiation alone, while later-stage disease should be treated with either whole pelvis radiation alone or whole pelvis radiation followed by intracavitary radiation. We used brachytherapy or external whole pelvis 45–50 Gy irradiation for patients with early stage disease and 55–60 Gy for patients with gross residual disease. For patients with clinically present tumor, much higher doses are needed theoretically, but such doses are difficult to administer externally in the pelvis mainly because of the radiosensitivity of the bowel.

To control for higher relapse rate of gross residual disease, the necessity of intracavitary radiation in addition to external radiotherapy (for higher dose delivery to residual tumor area and less bowel dose than external radiotherapy) is not confirmed[8-10, 22].

More data or prospective randomized trial to confirm this issue is necessary. We are planning to use multiagent preradiation chemotherapy to reduce tumor volume in patients with cancer of the cervix with gross disease present after a cut-through hysterectomy in hopes of better results than radiation alone.

The results of univariate analysis for prognostic factors suggest that retrospective stage, residual disease status, tumor histology are the significant prognostic factors. Many reported series agree with retrospective stage and residual disease as prognostic factors but in regarding to tumor histology, there was no agreement[8, 12].

In conclusion, while the expectations for survival of patients with no gross disease are favorable with some complication, patients with gross residual disease (and probably full thichness involvement of cervix wall) remaining after hysterectomy appear to be markedly worse than comparable stage treated initially with radical radiation alone. Therefore most cases of inappropriate hysterectomy performed in the presence of invasive cancer must be avoided (especially in patients with gross residual disease) by careful adherence to well established guidelines for cervical cancer detection and also, precise staging and proper management is important first of all.

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= 국문초록 =

부적절한 수술후 침윤성 자궁경부암의 방사선치료 결과

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목 적 : 상피내암, 초기 침윤성 자궁경부암, 또는 양성 질환으로 자궁적출술 받은 후 침윤성 자궁경부암으로 확인되어 방사선치료를 받은 환자의 치료 결과와 예후를 분석 하고자 하였다.

대상 및 방법 : 1985년 9월부터 1993년 12월까지 수술후 침윤성 자궁암으로 진단되어 방사선치료를 시행한 61명의 환자를 대상으로 후향적 분석을 시행하였다. 수술전 진단은 상피내암이 가장 많았으며 (38명), 초기 침윤성 자궁암 (10명), 자궁근종 (6명)등이었다. 대부분 수술후 2개월 이내에 방사선치료를 시행하였으며 3명은 추적검사중 재발암으로 확인되어 치료하였다. 8명은 강내치료만을, 47명은 외부 방사선치료만을, 그리고 6명은 강내치료와 외부 방사선치료를 같이 시행하였다.

결 과 : 5년 생존율 및 무병 생존율은 각각 83.8%, 86.9% 였으며 수술 당시의 육안적 잔존병소가 있었던 경우는 38.4%로 매우 낮았다. 모두 8명의 치료실패가 있었으며 예후인자로는 후향적 병기, 잔존병소 유무, 병리조직유형이 있었다.

결 론 : 조기 침윤성 자궁암은 부적절한 수술후에도 방사선치료로 효과가 좋으나 잔존병소가 있는 경우에는 예후가 불량하므로 좀 더 적극적인 치료가 필요하며, 무엇보다도 조기에 정확한 검진과 병기 결정을 시행하여 각 병기에 따른 적절한 치료가 필요하다.