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Postoperative Adjuvant Chemotherapy for High Risk Carcinoma of Cervix Stage I_b

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ABSTRACT

Objective To assess rate of recurrence, overall survival rates in 'relatively' high risk invasive cervical cancer of FIGO stage I_b patients who received adjuvant oral chemotherapy after standard radical hysterectomy.

Design Retrospective descriptive analysis.

Setting Oncology unit, Department of Obstetrics-Gynecology. Siriraj Hospital.

Population Invasive cervical cancer of FIGO stage I_b patients from 1985 to 1998, whose pathological report were categorized to be 'relatively' high risk.

Result The evaluable patients included 43 cases. The study revealed 2 recurrent cases (4.6%) with 95% overall 5-year survival time.

Conclusion Postoperative adjuvant oral chemotherapy of 5-Fluorouracil and Mitomicin-C in 'relatively' high risk cervical cancer stage I_b patients is satisfactory in terms of recurrent rate and overall 5-year survival time.

Key words: cervical carcinoma, 'relatively' high risk, deep invasion, 5-Fluorouracil, Mitomicin-C

Definition

- 'Relatively' high risk : patients who underwent standard radical hysterectomy with pathological reports revealing deep invasion, presence of capillary-lymphatic space invasion. Lesion near parametrium, vaginal margin and lesion that involved lower uterine segment, internal os and serosa of cervix also included.
- Deep tumor invasion: invasion of tumor to at least half of cervical thickness.

Radical hysterectomy and bilateral pelvic

lymph nodes dissection is a standard treatment for stage Ib carcinoma of cervix with 5-year survival rate of 85%.[1] Prognostic risk factors that influence local recurrence or distant metastasis are depth of invasion, presence of nodal metastasis, microcopic parametrial involvement and positive or close surgical margins.[2] These risk factors are associated with higher recurrence and reduction of survival. Metastasis to pelvic lymph nodes decreased survival substatially ans is considered to be the single most important factor that has survival impact. However, in the absence of node metastasis, 7% pelvic recurrence still ocuured as reported by Gonzales et al.[4] More than one-third of recurrence also presents with extrapelvic diseases.[5] To improve survival rate of these patients adjuvant therapy had long been explored.

To consider whether adjuvant treatment should be given or not, depends mainly on pathological reports of specimen which categorized patients into high risk and low risk groups. High risk patients include those of positive pelvic, para-aortic lymph nodes, parametrial invasion or positive surgical margins. Adjuvant treatment are generally given in high risk patients, which could be radiotherapy, chemotherapy or chemoradiotherapy. Low risk patients are simply patients who do not in high risk category.

There is another group of patients who are 'relatively' high risk for disease relapse. They are patients with pathological report of lesion 'close to' parametrium, vaginal margins, or serosa of cervix. Lesion involved lower uterine segment, deep invasion, or presence of capillary-lymphatic space invasion are also included in 'relatively' high risk patients.

5-Fluorouracil in said to be one of the drugs that is active against squamous cell carcinoma with 18 – 20% activity in advanced or recurrent cervical carcinoma.[6] The drug is given intravenously but considering ease of administration, we selected oral form for adjuvant treatment in the 'relatively' high risk cervical carcinoma patients. Mitomicin-C is another cytotoxic drug used for cervical carcinoma.[6] It should be used intravenously, but as mentioned due to ease of administration, we delivered oral form to these patients.

Since there is no general guide line management in these patients, long-term oral 5-Fluorouracil and/or Mitomicin-C had been used as postoperative adjuvant treatment in poor prognostic risk invasive cervical cancer of FIGO stage I at Siriraj Hospital since 1984, until now in order to minimize the recurrent risk and improve survival. This retrospective study was aimed to assess the results of oral chemotherapy which had been used at the institution.

Methodology

Review medico-surgical files from 1985 to 1998 of invasive cervical cancer carcinoma of stage I_b patients both squamous cell carcinoma and adenocarcinoma with histology evidence of having deep cervical stromal invasion, and/or presence of capillary-lymphatic space invasion and other risk factors indicated in 'relatively' high risk patients. Prior neoadjuvant chemotherapy or irradiation before standard surgery

- Recurrent carcinoma of cervix
- Postoperative intravenous chemotherapy (prior to oral chemotherapy)
- Co-existence with other malignacy (Two primaries)
- Positive pelvic lymph nodes, occult parametrial metastasis, or positive vaginal margins. (underwent postoperative irradiation)

All patients received oral chemotherapy with 5-Fluorouracil and Mitomicin-C in the dose of 200 mg/d and 2 mg/d respectively for 7 days in 4 weekly intervals for at least 6 courses. Complete blood and platelet counts were performed for each visit at out-patient gynecologic oncology unit. An absolute neutrophils counts 1,500 and platelet counts 100,000 /mm^3 implied sufficient bone marrow activity and oral chemotherapy were continued as maintainance dose for at least 6 courses. Side effects of chemotherapy were also recorded. The patients were followed up monthly for 6 months and 2-3 monthly for one year and 3-4 monthly for the second year and 6 monthly for

subsequent years until after 5 years when a yearly visit is advised. Pelvic examination and Papanicolaou smear was done at 3 monthly intervals in the first year and subsequently at every visit. Those who were included in the criteria and later lost follow up, postcards or telephones were used to acknowledge their well-beings.

The collected data were compiled and statistic calculation was done in terms of mean, standard deviation, recurrent rate. Kaplan-Meier was used to assess the concerned results i.e. overall free survival time.

Population

Invasive cancer of cervix of FIGO stage I_b patients who received post-opevative long-term oral chemotherapy with 5-Fluorouracil and Mitomicin-C after standard radical hysterectomy with pathological reports including one or more of the followings: deep cervical stromal invasion, presence of capillary-lymphatic space invasion, lesion near parametrium, vaginal margin and lesion that involved lower uterine segment, internal os or serosa of cervix.

Methodology

Review medico-surgical files of invasive carcinoma of cervix stage I_b patients both squamous cell carcinoma and adenocarcinoma with histology evidence of having deep tumor invasion, and/or presence of capillary-lymphatic space invasion and other risk factors indicated in inclusion criteria. All patients received oral chemotherapy with 5-Fluorouracil and Mitomicin-C in the dose of 200 mg/d and 2 mg/d respectively for 7 days in 4 weekly intervals for at least six courses. Complete blood and platelet counts were performed for each visit at out-patient gynecologic oncology unit. An absolute neutrophils counts $\geq$ 1,500 and platelet counts $\geq$ 100,000 /mm^3 implied sufficient bone marrow activity and oral chemotherapy were continued as maintainance dose for at least 6 courses. Side effects of chemotherapy were also recorded. The patients were followed up monthly for 6 months and 2-3 monthly for one year and 3-4 monthly for the second year and 6 monthly for subsequent years until after five years when a yearly visit is advised. Pelvic examination and Papanicolaou smear was done at three monthly intervals in the first year and subsequently at every visit. Those who were included in the criteria and later lost follow up, postcards or telephones were used to acknowledge their well-beings.

The collected data were compiled and statistic calculation was done in terms of mean, standard deviation. Kaplan-Meier was used to assess the concerned results i.e. disease free survival rates.

Results

There were collectively 96 files of patients who received oral chemotherapy with Mitomycin C and 5-Fluorouracil since 1985. Out of 96 patients, 53 patients were excluded from the retrospective study due to exclusion criteria mentioned earlier. All 43 selected-patients had pathological reports of deep invasion of carcinoma, among these 3 patients had deep invasion of carcinoma near serosa of cervix. Out of 43 patients, 11 had lymph vascular space invasion, one lesion near parametrium, two lesions near vaginal margin, three lesions extended to lower uterine segment, and one with lesion at level of internal os. One patient who had lesion near parametrium also involved lower uterine segment. Thirty-six patients had squamous cell carcinoma of cervix, five adenocarcinoma and two adenosquamous cell carcinoma.

Upon follow up, 41 out of 43 patients were survived without disease with mean minimal disease free survival of 72.24 months $\pm$ 44.08 SD. Only 2 out of 43 patients had disease recurrence 3 and 7 months after surgery i.e. after second and six courses of chemotherapy. The overall disease free survival rate was 69.11 months $\pm$ 45.34 SD. Recurrent rate was 4.6%.

Among two cases of recurrence, both had deep invasion carcinoma with one that invade near serosa of cervix. There were no additional risk factors. Both

had local recurrence proved pathologically. Patients were transferred for irradiation.

All patients tolerated well with oral chemotherapy without nausea, vomiting, hair-loosing or even weakness. There was no anemia or significant bonemarrow suppression detected.

Kaplan-Meier graph revealed 95% cumulative 5 year survival rate.

Table 1. Rick Factors

Risk Factors	Number of Patients
• Deep Invasion	43
(i) Squamous cell carcinoma	36
-Lower Uterine Segment Involvement	3/36
-Internal Os Involvement	1/36
-Tumor Near Serosa of Cervix	3/36
(ii) Adenocarcinoma	5
(iii) Adenosquamous cell carcinoma	2
• Lymph Vascular Space Invasion	11/43
• Tumor Close to Parametrium	1/43
• Tumor Near Vaginal Margin	2/43

Table 2. Rick Factors

Risk Factors	Mean Disease Free Survival**** (month), (Min.,Max)
Deep Invasion	72.1 (3, 185)
Lymph Vascular Space Invasion (LVS)	54.6 (18, 145)
Tumor Close to Parametrium *	18.0 (18, 18)
Tumor Close to Vaginal margin**	19.0 (17, 21)
Other Risks	
• Adenocarcinoma cell type	53.2 (21, 72)
• Adenosquamous cell type	38.0 (17, 59)
• Squamous cell type	
Lower Uterine Segment Involvement***	30.3 (18, 54)
Internal Os Involvement	145.0 (145, 145)
Tumor Near Serosal Surface***	63.0 (7, 65)

* Surgery was performed in 1997.

** Surgery was performed in 1997.

*** One patient with lower uterine segment involvement also had tumor near serosal surface.

**** Mean duration of survival in term of months from date of surgery to last follow up

Table 3. Mean Survival Time* (Month)

Numbers	Mean	Standard Deviations
41	72.24	44.08
2	5.00	2.82
43	69.11	45.34

* Mean interval in term of months from date of surgery to date of detected recurrence or duration of survival without recurrence to last follow up

Discussion

Presently there is no definite guideline for patients who are at increase risk of relapse after radical hysterectomy and pelvic lymphadenectomy. Options could be observation, pelvic radiotherapy, chemoradiotherapy, and adjuvant chemotherapy. The choices differs under physician consideration, depending on pattern of failure one would expect, locoregional or distant metastasis, specific risks may hints specific pattern of failure.[7,8,9]

Reports of retrospective study demonstrated pattern of recurrence after radical hysterectomy and pelvic lymphadenectomy for stage IB/IIA cervical cancer, 42% have pelvic failure, 28% have distant failure, while 30% have both components of failure.[8-14]

Pelvic irradiation has been the most commonly used adjuvant therapy. In the report of Guttman,[15] pelvic relapse is reduced in 21 of 22 patients with positive or close surgical margins. Most reports also confirm a reduction in pelvic relapse with postoperative radiotherapy.[9,10,16-19] Kinney et al, conducted a match-pair analysis for postoperative radiotherapy in patients matched for prognostic risk factors, he concluded that adjuvant pelvic radiation reduced pelvic failure from 67% to 27%. The median time to recurrence was 2.1 years compared to 1.4 years in non-radiated patients.

Despite convincing evidence in reduction of pelvic recurrence with postoperative radiation, there is no evidence in improvement of survival rates. Approximately 60% of patients also have disease recurrence beyond the pelvis. Eventhough lymph nodes positivity is the strongest single predictor of recurrent risk after surgery, an equal number of deaths occur in node-negative group and the relapse more commonly at locoregional sites; whereas the node-positive group exhibits a greater proportion of distant failure.[9,10,16,18,19]

Since 28% of patients failed with distant metastasis alone. There are trials for postoperative systemic intravenous chemotherapy and Cisplatin is claimed to be most effective with response rate ranging between 20% and 45%.[12,13] Various chemotherapeutic regimens have been used but there was no apparent decrease in distant metastasis rate or survival improvement.

There are trials for efficacy of oral chemotherapy in carcinoma of cervix. Wada and Koyama did a retrospective comparative study on efficacy of long-term oral maintenance chemotherapy (Fluorouracil) in high risk carcinoma of cervix. The patients are divided into squamous cell carcinoma group and adenocarcinoma group. All patients received more than 300 mg/day of antimetabolite tablets for one year or more after the main therapy. The Kaplan-Meier overall and cancer specific survival analysis estimates that the chronic administration of antimetabolites did not improve the cumulative 5-year survival in the SCC group. In contrast, the cumulative 5-year survival rate in the adenocarcinama group treated with antimetabolites (88%) was significantly higher than that without chemotherapy (64%) by Kaplan-Meier analysis. This significant improvement in the survival rate in the adenocarcinoma group due to antimetabolites was notable in patients in FIGO stage I or II treated with

radical or semiradical hysterectomy. He concluded that oral adjuvant chemotherapy with antimetabolites is useful for cervical adenocarcinoma, but not for squamous cell carcinoma.[6]

Anticancer activity of oral Mitomycin-C and 5-Fluouracil was confirmed by the report from another trial conducted in our hospital. It was a controlled study to evaluate the efficacy of concomitant oral chemotherapy with radiation in carcinoma of cervix stage IIB and IIIB which indicated an improvement in local control using the combined therapy : 83.3% vs 66.6% in stage IIB and 78.5% vs 41.6% in stage IIIB. The toxicity and side effects of the combination therapy were minimal.[20]

At Siriraj Hospital, patients of high risk carcinoma of cervix stage IB i.e. positive lymph node metastasis, positive vaginal margin, positive parametrial invasion, are advised for adjuvant radiotherapy. Patients with deep stromal invasion, presence of capillary-lymphatic space invasion, lesions near parametrium or vaginal margin, lesions that involved lower uterine segment, internal os or serosa of cervix would be allocated this to undertake oral chemotherapy protocol.

In this study all patients tolerated well with oral chemotherapy. No side effects of nausea-vomiting, hair-loosing, or even weakness were reported. All patients could attend the follow up clinic on schedule without anemia or significant bone-marrow suppression. Recurrent rate in study is 4.6% compared to theoretical rate of 15% without adjuvant treatment and 5-year disease free survival is 95% indicate satisfactory result of oral chemotherapy in high risk patients. Nevertheless, a much larger studied population should be employed for more discrete conclusion.

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