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Results of Postoperative Treatments in View of the Surgical Stage of Uterine Endometrial Carcinoma

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Background : The indications for and the optimal mode of adjuvant therapy in surgically operated endometrial cancer patients have not yet been established. We studied the indications for the postoperative treatment of endometrial carcinoma patients based on their surgical stages (FIGO, 1988) .

Methods : We retrospectively restaged the cases of 178 endometrial carcinoma patients who underwent hysterectomy with pelvic lymphadenectomy between 1965 and 1992 and who were followed-up longer than 3 years. The patients were subdivided into low- and high-risk groups, and we investigated the relation between their postoperative treatment and recurrence rates. Postoperative treatment was divided into the three groups of no/incomplete, external whole-pelvic irradiation (EWPI) and chemotherapy.

Results : The 79 patients in Stage Ia or Ib had no/incomplete postoperative treatment, but only 1 (1.3%) had a recurrence. Four Stage IIa patients had no recurrence and all 3 low-risk patients had no postoperative treatment. Of the 5 Stage IIb, low-risk patients, 1 of the no postoperative-treatment group had a recurrence. The recurrence rate among the Stage IIb patients of the high-risk group was 40% (2/5) in the incomplete postoperative treatment group. The six Stage IIIa patients with EWPI had no recurrence. In contrast, 14 of the 15 Stage IIIb and IIIc patients underwent postoperative EWPI, and 11 of them (78.6%) had a recurrence including 8 (81.8%) with a recurrence in distant regions.

Conclusion : Postoperative treatment may be well omitted for many patients at Stage Ia or Ib and the low-risk group at Stage IIa based on surgical staging criteria. Patients in other surgical stages seemed to require to identify best postoperative treatment , but further randomized prospective studies will be required to identift the best mode of treatment.

Key words : Endometrial carcinoma, Surgical stage, Postoperative treatment, Recurrence

Introduction

In 1988, the International Federation of Gynecology and Obstetrics (FIGO)[1)] issued a system of surgical staging for endometrial carcinoma. According to this system, a determination the surgical stage is made based on the findings by laparotomy as well as on the routine clinical examinations. Thus, laparotomy, hysterectomy and biopsies of all suspicious sites form the bases for staging. The final histologic findings after surgery (and cytologic findings when available) are also to be considered in the staging. However, the previously accepted FIGO guidelines for clinical staging (1983) are still relevant and should be used for the patients not primarily operated and those treated with radiation and/or chemotherapy. Accordingly, the surgical staging is not a substitute for the clinical staging. The clinical staging system has already been applied widely in Japan, and the surgical staging system was also accepted by the Committee on Gynecology and Oncology of the Japan Society of Obstetrics and Gynecology[2)] in January 1996.

Since the surgical stage refers to the presence and degree of the major prognostic factors obtained histologically in endometrial carcinoma[3-5)], the surgical stage is considered to reflect prognosis better than the conventional clinical stage and can be used to individualize an appropriate postoperative therapy. In the present study, we retrospectively analyzed a series of endometrial carcinoma patients to determine the relationship between postoperative treatments and recurrences by surgical stage.

Patients and Methods

As histological prognostic factors for endometrial carcinoma, the presence of vessel permeation[3,6-8)] and specific histologic types[3,4,8-10)] (adenosquamous carcinoma, clear cell adenocarcinoma, serous adenocarcinoma, mucinous adenocarcinoma, squamous cell carcinoma, undifferentiated carcinoma, and carcinosarcoma) have been established in addition to the factors involved in the surgical staging (histologic differentiation, depth of myometrial invasion, cervical involvement, vaginal or adnexal invasion, and lymph node metastasis). Thus, for the carcinomas at the same surgical stage, the presence of vessel permeation and specific histologic types may be important prognostic factors histologically.

We examined the cases of 178 patients who underwent

hysterectomy with pelvic lymphadenetomy for endometrial carcinoma between 1965 and 1992 at the Nagasaki University School of Medicine. The patients were 25-76 years of age, mean 53.0±10.6 years. We performed a surgical staging on the 178 cases retrospectively, and for each stage (Stage I in 126 cases, Stage II in 27 cases, and Stage III in 25 cases), the relation between postoperative treatments and recurrence was studied in two groups, the low-risk group and the high-risk group (Table 1), which were based on the histological prognostic factors not directly related to staging. This patients series included neither the cases in the low-risk group under Stage III nor those under Stage IV by surgical staging.

The histologic types and histologic differentiation were diagnosed according to the histologic classification of "The General Rules for Clinical and Pathological Management of Uterine Corpus Cancer"[2]. For the sake of convenience, the cases which corresponded to recurrence and relapse as definded in "The General Rules for Reporting on Clinical Oncology"[11] were studied collectively as the recurrent cases in this study.

For the 151 patients treated in or after 1972, as a rule, the selection was made regarding the mode of operation and postoperative external irradiation (^{60}Co whole-pelvic irradiation) based on clinical stages and histologic differentiation (Table 2). For some of the patients among them, chemotherapy mainly consisting of Mitomycin C (MMC) [MMC alone or MMC+gestagen (4 patients), and 5-fluorouracil+Cyclophosphamide+MMC in combination (FAM) or FAM+gestagen (5 patients)] was applied as a substitute for the external irradiation. For the 27 patients treated in or before 1971, simple hysterectomy and bilateral adnexectomy, as well as the combination of these modes of operation with pelvic lymphadenectomy or radical hysterectomy, were performed, wherein 9 patients had external irradiation (8 patients) and MMC administration (1 patients), additionally. The patients who underwent extrapelvic radiation therapy in a total dosage

Table 1. Endometrial carcinoma patients treated between 1965 and 1992 at the Nagasaki University School of Medicine: low-and high-risk groups at each surgical stage.

Surgical stage (Cases)	Histological prognostic factor				Groups(Cases)
	Depth of myometrial invasion	Histologic differentiation	Vessel permeation	Histologic type	
Stage I (126)	Stage Ia (none), Ib (≦1/2) or	Grade 1	−	Endometriod, Adenoacanthoma	Low-risk group*(70)
	Ic (>1/2)	Grade 2,3	+	Specific type	High-risk group**(56)
Stage II (27)	None, ≦1/2	Grade 1	−	Endometriod, Adenoacanthoma	Low-risk group*(8)
	>1/2	Grade 2,3	+	Specific type	High-risk group**(19)
Stage III (25)	None, ≦1/2	Grade 1	−	Endometriod, Adenoacanthoma	Low-risk group*(0)
	>1/2	Grade 2,3	+	Specific type	High-risk group**(25)

* Consisting of cases that met all of the histologic prognostic factors.
** Consisting of cases in which one or more prognostic factor was associated.

Table 2. Selection of the surgical mode based on clinical stage and histologic differentation, and indication for postoperative irradiation.

Clinical stage	Histologic differentiation	Surgical mode	Indication for postoperative irradiation
Stage I	Grade 1, 2	MRH*with pelvic lymphadenectomy	Case with 1, 2, and/or 3 1. Invasion to over 1/3 of myometrium 2. Carvical involvement 3. Lymph node metastasis
	Grade 3	RH**	All cases
Stage II, III	Grade 1, 2, 3	RH**	All cases

* MRH : Modified radical hysterectomy
** RH : Radical hysterectomy

Table 3. Recurrence rate at each surgical stage among 178 endometrial carcinoma patients.

Surgical stage	No.	Recurrence				
		No.	Rate(%)			
Ia	36	0	0			
Ib	64	1	1.6	3.2		
Ic	26	3	11.5		*	
IIa	4	0	0			***
IIb	23	6	26.1	22.2		
IIIa	10	2	20.0		**	
IIIb	1	1	100	56.0		
IIIc	14	11	78.6			
Total	178	24	13.5			

* p=0.0023, **P=0.0217, ***P<0.0001

Table 4. Recurrence in the Stage I (low-risk group) patients by postoperative treatment.

Surgical stage	No/incomplete		External irradiation		Chemotherapy		Total	
	No.	No. of recurrences	No.	No. of recurrences	No.	No. of recurrences	No.	No. of recurrences
Stage Ia	24	0	1	0	0		25	0
Stage Ib	27	0	7	0	3	0	37	0
Stage Ic	2	0	5	0	1	0	8	0
Total	53	0	13	0	4	0	70	0

of not more than 50 Gy (at point A) and those who underwent the MMC chemotherapy in a total dosage of not more than 40 mg were both included in the no/incomplete postoperative therapy group.

Thus, the postoperative therapy was studied after dividing the patients into 3 groups, namely, the extrapelvic radiation therapy group (70 patients), the chemotherapy group (10 patients), and the no/incomplete postoperative therapy group (98 patients).

Results

The prognosis for at least 3 years or longer was confirmed in all 178 of the patients enrolled as subjects in this study, wherein 24 patients (13.5%) revealed a recurrence histologically or clinically. Recurrence in the surgical stage was noted in 4/126 patients (3.2%) in Stage I, 6/27 patients (22.2%) in Stage II, and 14/25 patients (56.0%) in Stage III, with a significant difference among these 3 groups (Fisher's exact method) (Table 3). Further, when subdivided to each stage, an increasing trend of recurrence was noted according to the development of the lesion. Based on the surgical stages, the results studied in comparison with the postoperative therapy administered are explained below.

1. Surgical Stage I

1) Low-Risk Group in Stage I

In the low-risk group in the Surgical Stage I (70 patients), no recurrence has been noted to date, and a fairly good number of patients, i.e., 24 of the 25 patients in Stage Ia and 27 of the 37 patients in Stage Ib have been treated by surgical operation alone (Table 4).

Among the patients in whom the depth of myometrial invasion was over ½ (Stage Ic), 5 of the 8 patients required external whole-pelvic irradiation and 1 patient needed MMC administration additionally, even though they belonged to the low-risk group, and no recurrence has been noted in them so far. Recurrence was also not noted in the 2 patients of the no/incomplete postoperative therapy group.

2) High-Risk Group in Stage I

Eleven patients of the high-risk group at Stage Ia have not shown recurrence yet, including 10 patients treated with a surgical operation alone (Table 5).

In contrast, of the 18 patients at Stage Ib and 6 at Stage Ic, who underwent no or incomplete additional postoperative treatment, one patient (5.6%) and 2 patients (33.3%) showed recurrence, respectively (Table 5). Of the 21 patients with additional external whole-pelvic irradiation or MMC administration, recurrence has been observed in only 1 patient (4.8%).

2. Surgical Stage II

Among the Stage IIa patients, 3 of the low-risk group patients had no postoperative treatment at all, and 1 patient of the high-risk group had postoperative treatment

Table 5. *Recurrence in the Stage I (high-risk group) patients by postoperative treatment.*

Surgical stage	No/incomplete			External irradiation			Chemotherapy			Total		
	No.	Recurrence		No.	Recurrence		No.	Recurrence		No.	Recurrence	
		No.	Rate(%)		No.	Rate(%)		No.	Rate(%)		No.	Rate(%)
Stage Ia	10	0	0	1	0	0	0			11	0	0
Stage Ib	18	1[a]	5.6	9	0	0	0			27	1	3.7
Stage Ic	6	2[b]	33.3	11	1[c]	9.1	1	0	0	18	3	16.7
Total	34	3	8.8	21	1	4.8	1	0	0	56	4	7.1

[a, c] Recurrence in distant region
[b] Recurrence in pelvic cavity (1 patient), and recurrence in distant region (1 patient)

Table 6. Recurrence in the Stage II (low-risk group) patients by postoperative treatment.

Surgical stage	No			External irradiation			Total		
	No.	Recurrence		No.	Recurrence		No.	Recurrence	
		No.	Rate(%)		No.	Rate(%)		No.	Rate(%)
Stage IIa	3	0	0	0			3	0	0
Stage IIb	1	1[a]	100	4	0	0	5	1	20.0
Total	4	1	25.0	4	0	0	8	1	12.5

[a] Recurrence in vagina

Table 7. Recurrence in the Stage II (high-risk group) patients by postoperative treatment.

Surgical stage	No/incomplete			External irradiation			Chemotherapy			Total		
	No.	Recurrence		No.	Recurrence		No.	Recurrence		No.	Recurrence	
		No.	Rate(%)		No.	Rate(%)		No.	Rate(%)		No.	Rate(%)
Stage IIa	0			1	0	0	0			1	0	0
Stage IIb	5	2[a]	40.0	11	2[b]	18.2	2	1[c]	50.0	18	5	28.7
Total	5	2	40.0	12	2	16.7	2	1	50.0	19	5	26.3

[a] Recurrence in distant region (1 patient), and recurrence in pelvic cavity (1 patient)
[b] Recurrence in pelvic cavity (1 patient), and recurrence in distant region (1 patient)
[c] Recurrence in vagina

by external whole-pelvic irradiation, and no recurrence has been observed in any of these four patients (Tables 6 and 7).

Of the 5 cases in Stage IIb of the low-risk group, 1 patient with no postoperative treatment had a vaginal recurrence, but the other 4 patients with external whole-pelvic irradiation showed no recurrence (Table 6). Of the 18 cases in Stage IIb of the high-risk group, 3 of the 13 patients (23.1%) who underwent irradiation or chemotherapy had recurrence (Table 7). Two of these 3 patients with a recurrence had postoperative treatment by whole-pelvic irradiation, but both of them developed the recurrence in the pelvic cavity of the irradiated field.

3. Surgical Stage III

All of the 25 patients at surgical Stage III belonged to the high-risk group and included no patient in the low-risk group (Table 1). Of these 25patients, 23 completed postoperative treatment by external whole-pelvic irradiation or FAM therapy, and 13 of these 23 patients with postoperative treatment (56.5%) had a recurrence. For 6 patients in Stage IIIa with external whole-pelvic irradiation, no recurrence has been observed so far (Table 8).

Table 8. Recurrence in the Stage III (high-risk group) patients by postoperative treatment.

Surgical stage	No/incomplete			External irradiation			Chemotherapy			Total		
	No.	Recurrence		No.	Recurrence		No.	Recurrence		No.	Recurrence	
		No.	Rate(%)		No.	Rate(%)		No.	Rate(%)		No.	Rate(%)
Stage IIIa	2	1	50.0	6	0	0	2	1	50.0	10	2	20.0
Stage IIIb	0			1	1	100	0			1	1	100
Stage IIIc	0			13	10	76.9	1	1	100	14	11	78.6
Total	2	1[a]	50.0	20	11[b]	55.0	3	2[c]	66.7	25	14	56.0

[a] Recurrence in pelvic cavity
[b] Recurrence in distant region (7 patients), distant region and pelvic cavity (2 patients), pelvic cavity (1 patient), and unknown (1 patient)
[c] Recurrence in distant region and pelvic cavity (1 patient), and recurrence in pelvic cavity (1 patient)

In the Stage IIIb and IIIc groups, postoperative treatment was applied to all 15 patients, and 14 of them had external whole-pelvic irradiation. However, 11 of these 14 patients (78.6%) had a recurrence, and 9 of them (81.8%) were in the distant region and, in some cases, included a pelvic cavity recurrence (Table 8).

Discussion

The optimal mode of treatment for endometrial carcinoma has not yet been established by a unified consensus, which is different from the situation for cervical carcinoma or ovarian carcinoma. For instance, in Europe and the U.S.A., preoperative irradiation for endmetrial carcinoma has been applied frequently, which, however, has often reviewed negatively regarding its usefulness, because of the changes caused in the pathohistological images useful for the selection of treatment and as prognostic indicators, and because it does not much improve the therapeutic results compared with those by postoperative irradiation[4,12-15]. The indications or mode of postoperative treatment for endometrial carcinoma have also not been established. To prevent such chaos in the management of endometrial carcinoma, it is necessary to use the FIGO surgical staging system, which incorporates important histopathological prognostic factors and accurately reflects prognosis, as confirmed by many researchers[3-5] and our present results; it is also important to prospectively compare, based on the FIGO system, the results produced by various modes of treatment.

Ackerman et al[16]. analyzed the relapse pattern in clinical Stage I endometrial carcinoma patients and indicated the inappropriateness of applying adjuvant pelvic irradiation as a routine technique to the patients with Grade 1 or 2 endometrial carcinoma with less than 1/2 myometrial invasion or Grade 3 tumors confined to the endometrium. In our present study, of the 79 patients at surgical Stage Ia (tumor limited to endometrium) and Ib (invasion to $\leqq 1/2$ myometrium) treated surgically (simple or modified radical hysterectomy with pelvic lymphadenectomy) with no/incomplete postoperative treatment, only one patient (1.3%) had recurrence. This recurrent patient (surgical Stage Ib, Grade 2 endometrioid adenocarcinoma) was in Stage Ib of the high-risk group and was one of the 18 patients (5.6%) with no/incomplete postoperative treatment. These results indicate the possibility that the patients diagnosed as Stage Ia or Ib by surgical staging can often be cured without postoperative treatment regardless of the grade of histologic differentiation, presence or absence of vessel permeation, or histologic type.

In the surgical Stage Ic (invasion$>1/2$ myometrium) gruop, 8 patients of the low-risk group had no recurrence regardless of the presence or absence of postoperative treatment. However, the sample number of this group was too small to make a definite conclusion, and we are thus now administering adjuvant whole-pelvic irradiation to all similar patients, as a rule. In Stage Ic of the high-risk group, 2 of the 6 patients with incomplete postoperative treatment had a recurrence, and 1 of the 12 patients with postoperative treatment had a recurrence. The number of samples for these results is too small to draw a conclusion, but it seemed necessary to apply postoperative treatment to surgical Stage Ic carcinomas in the high-risk group. However, some researchers indicate that postoperative adjuvant pelvic irradiation may be unnecessary in the patients with deep myometrial invasion by surgical staging, but without extrauterine invasion[16,17]. Thus, the significance of postoperative treatment in Surgical Stage Ic should be further examined.

Surgical Stage II is subdivided into IIa (endocervical glandular involvement only) and IIb (cervical stromal invasion) by cervical involvement. Therefore, the degree of myometrial invasion should be considered in classifying

risk groups in surgical Stages IIa and IIb (Table 1). Fanning et al[18]. treated 12 patients at surgical Stage IIa in the low-risk group by operation alone with no recurrence. We also treated 3 Stage IIa patients in the low-risk group by operation alone and there has been no recurrence so far. These results indicate that the impact of endocervical glandular involvement alone may be considerably small. Therefore, in surgical Stage IIa, the indication of postoperative treatment can be decided depending on the degree of myometrial invasion, i.e., in the same manner as in surgical Stages Ia, Ib and Ic.

In surgical Stage IIb, Fanning et al[18]. also reported a high incidence of recurrence (5 of 8 cases) (62.5%) treated by operation alone, which is in accord with our results. Postoperative treatment seemed to be necessary in the surgical Stage IIb patients for both the low-risk and high-risk groups, and the problem remains as to what kind of technique should be used. In our results, external whole-pelvic irradiation was useful in the 4 Stage IIb patients of the low-risk group. Considering that all of the 5 recurrent patients in Stage IIb of the high-risk group reported by Fanning et al[18]. had extrauterine recurrence, it may be necessary to establish postoperative treatment for surgical Stage II patients.

In surgical Stage III, extrauterine invasion is found histopathologically and almost all the present such patients belonged to the high-risk group by our definition ; the choice of postoperative treatment will thus be an essential question. Schorge et al[19]. noted that postoperative external whole-pelvic irradiation was not useful for surgical Stage IIIa (tumor invasion to serosa and/or adnexa and/or positive peritoneal cytology) or IIIb (vaginal metastasis) patients. Our study results suggest the usefulness of this technique in 6 Stage IIIa patients. Since Stage IIIa mainly refers to intrapelvic invasion, the significance of postoperative whole-pelvic irradiation is worth further investigation.

In the surgical Stage IIIb and Stage IIIc (metastases to pelvic and/or paraaortic lymph nodes) patients of the present study, the postsurgical external whole-pelvic irradiation group frequently had an extrauterine recurrence ; extended-field irradiation or systemic chemotherapy would thus be a reasonable selection for postoperative treatment. Of the patients classified as surgical Stage IIIc by pelvic lymph nodes metastasis, 67% of the patients also have paraaortic lymph node metastases[20], and extended-field irradiation including paraaortic lymph nodes and whole abdominal irradiation are recommended.[21-23] However, few randomized prospective studies have been conducted on postoperative systemic chemotherapy in endometrial carcinoma, and its usefulness has not been fully demonstrated. Recent phase II studies of advanced or recurrent cases found that the combinations of etoposide, cisplatin and 5-fluorouracil[24], of paclitaxel and G-CSF, and of ifosfamide and mesna[26] were effective.

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