located in the tumor tissues. Cells with CIC character in squamous cell carcinoma are reported to be located in the outer layer of cancer nests,[29,30] contrasting with the absence of any specific location of CIC in endometrioid adenocarcinoma.

Diffuse expression of ALDH1 was found in some clinical cases of endometrioid adenocarcinoma (Fig. 1d). This appeared to be incompatible with the concept that CIC comprise a small population of cancer cells with multiple differentiations and long-term repopulation capabilities. In several reports, CIC markers were expressed in most tumor cells in clinical samples, such as ALDH1 in breast cancers.[20,31] When most tumor cells possess CIC character, the tumor character might become aggressive. Alternatively, ALDH1 might be a marker of undifferentiated cancer cells but not a CIC marker.

The clinical implication of ALDH1 expression was evaluated in 98 cases of endometrioid adenocarcinoma. The characteristics of patients, such as age and stage, in the current study were similar to those in a previous report,[32] indicating that the results obtained from the current study are commonly applicable to endometrioid adenocarcinoma worldwide. The present study showed that a high level of ALDH1 expression was correlated with T category, lymphatic invasion, resistance to chemotherapy, recurrence, and prognosis of patients. Patients with higher ALDH1 expression showed poorer prognoses than those with lower expression ($P = 0.015$ for DFS and $P = 0.010$ for OS), and high ALDH1 expression was an independent poor prognostic factor. These findings were consistent with the previous observation that a high percentage of ALDH1-expressing cells in most types of epithelial tumors, such as breast, lung, pancreatic, bladder, ovarian and prostate, is associated with a poorer outcome of these patients.[23–27] Thus, ALDH1 might be a common marker for CIC among cancers of various organs.

Endometrioid adenocarcinoma is the most common invasive malignancy of the female genital system, and novel therapeutic strategies targeting CIC would be necessary to improve cure rate. Very recently, Yang *et al.*[33] reported that LIN28 positively and let-7 negatively regulates ALDH1 expression in breast and ovarian cancers, and suggested that targeting ALDH1 expression via a LIN28/let-7 axis by small chemical compounds could be a therapeutic modality. Then, ALDH1 would be an effective target for therapies to CIC not only in breast and ovarian cancers but also in endometrioid adenocarcinoma of the uterus. Further studies on ALDH1 regulation may open a new therapeutic modality for endometrioid adenocarcinoma.

Acknowledgments

The authors thank Ms. Megumi Sugano, Ms. Etsuko Maeno and Ms. Takako Sawamura for their technical assistance. This work was supported by grants from the Ministry of Education, Culture, Sports, Science and Technology, Japan (No. 20590364, No. 20014010).

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doi: 10.1111/j.1349-7006.2011.01864.x

Ann Surg Oncol (2010) 17:1111–1117
DOI 10.1245/s10434-009-0892-8

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – GYNECOLOGIC ONCOLOGY

Endometrial Carcinoma with Extra-abdominal Metastasis: Improved Prognosis Following Cytoreductive Surgery

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ABSTRACT

Background. Incidence of endometrial carcinoma, the most common malignancy of the female pelvis, has been steadily increasing during the last three decades. The prognosis for stage IVb cases with extra-abdominal metastases is extremely poor, with no current consensus regarding treatment. The aim of the present study was to examine the benefits of cytoreductive surgery for such cases.

Methods. Clinicopathological features of 33 stage IVb cases of endometrial carcinoma diagnosed during the 1991–2008 study period were retrospectively reviewed utilizing clinical records. Cytoreduction was conducted in 30 cases.

Results. The median progression-free survival (PFS) and overall survival (OS) of those patients with optimal cytoreduction of their disease (with residual masses $\leq$ 2 cm), were significantly better than those with suboptimal reduction (with residual masses $>$ 2 cm), not only among the 15 stage IVb patients with only intra-abdominal metastasis (group I) ($P = 0.0003$ and 0.0007) but also among the 15 cases with extra-abdominal metastasis (group E) ($P = 0.013$ and 0.016). Multivariate Cox proportional-hazards analysis demonstrated that the adjusted hazard ratio (HR) for the maximum size of residual disease (>2 vs. $\leq$2 cm) was 10.4 [95% confidence interval (CI), 1.27–84.70, $P = 0.030$] in group I and 16.92 (95% CI, 1.41–203.09, $P = 0.026$) in group E.

Conclusions. This is the first demonstration that aggressive cytoreductive surgery for stage IVb endometrial carcinoma with extra-abdominal metastasis has a beneficial role. However, further investigation is still required to establish better standard therapy for stage IVb endometrial cancer.

Endometrial adenocarcinoma occurs most frequently during the reproductive and menopausal times of life. In the USA, uterine endometrial carcinoma is already the most common malignancy of the female pelvis and the fourth most common cancer in women, and increasing incidence of the disease has been apparent during the last three decades.[1] In approximately 75% of endometrial carcinoma cases the tumor is confined to the uterus [International Federation of Gynecology and Obstetrics (FIGO) stage I] and has a favorable prognosis.[1] The prognosis, however, worsens as the disease progresses. Although only 3–13% of all endometrial cancers are stage IV, these account for 23% of cancer-related deaths in the first year following diagnosis.[2–5]

Endometrial tumors with metastatic dissemination to the abdominal or to extra-abdominal sites are both classified as stage IVb. The prognosis for stage IVb patients is extremely poor, with the 5-year survival rate being roughly 5%.[1] Treatment for even early-stage endometrial cancer usually consists of hysterectomy, salpingo-oophorectomy, and retroperitoneal lymph node dissection, combined with adjuvant radiotherapy or chemotherapy. However, with advanced disease outside the pelvis, therapy options become limited and the results less favorable, leaving no good current consensus regarding treatment of stage IVb endometrial cancer.[1]

First Received: 25 September 2009;
Published Online: 8 January 2010

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For a different female reproductive tumor, advanced ovarian carcinoma, maximal cytoreductive surgery combined with chemotherapy has been demonstrated to improve chances of survival.[6,7] In advanced endometrial cancers with dissemination to the intra-abdominal cavity, the role of debulking surgery was analyzed and the survival rate was shown to be improved by cytoreductive surgery.[2,8–10]

However, the role of debulking surgery in advanced endometrial cancer with extra-abdominal metastasis has yet to be elucidated. In the current study, we examined the prognostic factors and the role of cytoreductive surgery in stage IVb endometrial carcinomas, especially in those cases with extra-abdominal metastasis.

PATIENTS AND METHODS

During the 18-year study period of 1991 to 2008, in the Department of Obstetrics and Gynecology at the Osaka University Hospital, Osaka, Japan, 625 endometrial carcinomas were diagnosed and staged. The study population was entirely Japanese.

The clinicopathological features of the collective stage IVb endometrial carcinoma cases were retrospectively reviewed utilizing clinical records, including physical examination notes, radiological reports, operative records, and histopathology reports. The histological diagnosis was made by authorized pathologists of the Department of Pathology of the Osaka University Hospital. Cytological diagnosis was performed for pleural effusions. The variables considered in this study were patient age, histology, metastatic sites, and diameter of largest residual mass.

In our department, the standard of care for stage IVb patients, after obtaining written informed consent, is to conduct exploratory laparotomy with the intent of performing a total abdominal hysterectomy, bilateral salpingo-oophorectomy, staging, and maximum cytoreduction. For analysis of the effects of this debulking surgery, patients were retrospectively divided into two groups. Group I (for "intra-abdominal") consisted of the cases with metastases beyond the pelvic region but limited to the intra-abdominal cavity as the sole reason for their stage IVb designation. Group E (for "extra-abdominal") had extra-abdominal metastasis, with or without intra-abdominal metastasis. Analysis of the effects that these factors had on survival rates was conducted by log-rank test. Overall survival (OS) curves were constructed using the Kaplan–Meier method and evaluated for statistical significance by log-rank test. A multivariate Cox proportional-hazards model was used to determine the significantly important factors for survival in stage IVb endometrial cancer. The results were considered to be significant when the *P*-value was less than 0.05.

Statements of Ethics and Conflicts of Interest

This retrospective study was approved by our Institutional Review Board and the Ethics Committee. The authors have no conflicts of interest regarding the research reported herein.

RESULTS

Clinicopathological Characteristics of Stage IVb Endometrial Cancers

During the 18-year study period, 625 patients were diagnosed with endometrial cancer. Comparing the two consecutive 9-year periods, during which roughly equal numbers of general patients were seen, there were 190 cases diagnosed from 1991 to 1999 and 435 cases during 2000–2008, representing an apparent 2.3-fold increase in endometrial cancers, although the exact incidence per 1,000 patients cannot be determined from our data system.

Thirty-three endometrial cancers patients were staged as IVb, representing 5% of the 625 endometrial cancer cases. Although the number of stage IVb cases increased 3.2-fold in the second half of the study period, the percentage of endometrial cancers that were stage IVb increased only 1.4-fold, exhibiting no statistical significance (Table 1). The median follow-up observation period was 13 months (range 2–57 months). The median patient age at diagnosis was 63 years (range 48–77 years).

The most common histological types of stage IVb tumors were endometrioid adenocarcinoma (73%), followed by serous adenocarcinoma (24%) and clear cell adenocarcinoma (3%). The 24 endometrioid adenocarcinomas consisted of 4 cases (17%) of grade 1, 9 cases (38%) of grade 2, and 11 cases (46%) of grade 3. Other aspects of the disease distribution of the cases are presented in Table 2. Extra-abdominal metastasis, with or without intra-abdominal lesions beyond the pelvis, was observed in 18

TABLE 1 Number of endometrial cancers diagnosed during 1991–2008

	Former period (1991–1999)	Latter period (2000–2008)	Total (1991–2008)
Endometrial cancer	190	435	625
Stage IVb disease	8 (4%)	25 (6%)	33 (5%)

TABLE 2 Distribution of metastatic disease of stage IVb endometrial cancer cases

Anatomic region with metastasis	Number of cases	%
Retroperitoneal lymph node	18	55
Abdominal peritoneum	14	42
Omentum	13	39
Lung	8	24
Bowel serosa or mesentery	7	21
Liver	7	21
Pleural effusion with positive cytology	5	15
Supraclavicular lymph node	5	15
Ovary/fallopian tube	4	12
Inguinal lymph node	2	6
Spleen	1	3

TABLE 3 Surgical procedures performed for stage IVb endometrial cancer cases

Procedure	Number of cases	%
Hysterectomy and salpingo-oophorectomy	28	93
Retroperitoneal lymph node dissection	16	53
Omentectomy	14	47
Peritoneal implant excision ablation	14	47
Bowel resection	4	13
Supraclavicular lymph node dissection	2	7
Liver resection	2	7
Lung resection	1	3
Inguinal lymph node dissection	1	3

cases (group E), and intra-abdominal dissemination beyond the pelvis without extra-abdominal lesions was observed in 15 cases (group I). The extra-abdominal sites of metastatic involvement in the 18 patients were in five different locations: lungs (8 cases), liver (7 cases), pleural effusion (confirmed by cytology) (5 cases), supraclavicular lymph nodes (5 cases), and inguinal lymph nodes (2 cases). The clinical characteristics in our patient population were comparable to those of previous reports.[2,8,9]

Of the 33 cases, cytoreductive surgery was conducted in the 30 whose performance status was 0 or 1. The surgical procedures performed are listed in Table 3. Only palliative care was provided for the three remaining patients, one because she refused cytoreductive surgery and the other two because they had performance status of 3 due to extensive disease at time of diagnosis. These three cases were therefore excluded from our analysis of the effects of cytoreductive surgery.

The 30 patients who underwent cytoreductive surgery also received postoperative chemotherapy. Twenty patients had combination chemotherapy using taxane (paclitaxel), epirubicin, and carboplatin (TEC), or taxane and carboplatin without epirubicin (TC); ten patients received adjuvant chemotherapy in the form of combination of cisplatin, adriamycin, and cyclophosphamide (CAP), CPT-11 alone, or oral medroxyprogesterone acetate.

Analysis of Prognostic Factors in Stage IVb Endometrial Cancers

The median overall survival rate (OS) for patients older than 70 years was 8 months, statistically shorter than the OS of 26 months for those younger than 70 years ($P = 0.012$ by log-rank test) with a median follow-up of 13 months (range 2–57 months) (Table 4). The patients with endometrioid adenocarcinoma tended to survive longer than those with other types, including serous and clear cell adenocarcinomas; however, this tendency was not found to be

TABLE 4 Median OS by selected variables for stage IVb endometrial cancer

Variable	Number (cases)	Median OS (months)	*P*-value[a]
Age (years)			0.012
<70	23	26	
≥70	10	8	
Histology			0.074
Endometrioid	24	26	
Serous, clear cell	9	11	
Distribution of disease			0.73
Group I	15	22	
Group E	18	20	
Number of regions with metastasis			0.54
≤2 regions	15	41	
≥3 regions	18	13	
Surgery			<0.0001
Performed	30	22	
Not performed	3	2	
Maximum size of residual tumors[b]			<0.0001
≤2 cm	20	43	
>2 cm	13	6	
Postoperative chemotherapy			<0.0001
Performed	30	22	
Not performed	3	2	

Patient age, surgery performed, maximal size of postcytoreductive residual disease, and chemotherapy performed demonstrated statistically significant effects on the median OS for stage IVb endometrial cancers ($P = 0.0012$, <0.0001, <0.0001, and <0.0001, respectively, by log-rank test); however, histology and distribution of disease did not exhibit a significant association with prognosis

Group I: intra-abdominal metastasis alone; group E: extra-abdominal metastasis, alone or with both intra- and extra-abdominal metastases

[a] By log-rank test

[b] Three cases in which surgery was not performed were categorized into the group of maximum size of residual tumor >2 cm

statistically significant ($P = 0.074$ by log-rank test). Categorization of type 1 tumors, which consisted of endometrioid adenocarcinomas of grades 1 and 2, and type 2 tumors, which included a grade 3 endometrioid adenocarcinoma, a serous adenocarcinoma, and a clear cell adenocarcinoma, also failed to predict prognosis ($P = 0.53$ by log-rank test, data not shown).

The median OS for group I (with proximal intra-abdominal metastasis alone) and group E (with extra-abdominal metastasis, alone or with intra-abdominal metastasis) was 22 and 20 months, respectively, exhibiting no statistically significant difference ($P = 0.73$ by log-rank test). Having pleural effusion with positive cytology did not relate to OS significantly either ($P = 0.46$ by log-rank test, data not shown). The number of anatomical regions with metastasis also did not associate with OS ($P = 0.54$ by log-rank test).

Surgery and postoperative chemotherapy were performed in 30 cases, and the prognosis of those patients was better than that of the cases in which surgery and chemotherapy were not performed ($P < 0.0001$ by log-rank test). The median OS for the cases where the diameter of the largest postcytoreductive residual disease was relatively small (≤2 cm) was significantly better than that for the cases with larger (>2 cm) residual disease ($P < 0.0001$ by log-rank test).

Effect of Cytoreductive Surgery for Stage IVb Endometrial Cancers with Only Intra-abdominal Metastasis (Group I)

Debulking surgery was conducted for the 15 group I cases, with the intent of removing as many of the largest disseminated tumors as possible. The surgery was considered to be a "suboptimal cytoreduction" if lesions larger than 2 cm were left behind. Suboptimal cytoreduction occurred in 5 of the 15 patients (33%). The procedure was considered to be "optimal cytoreduction" when the residual lesions were only ≤2 cm in maximal diameter. Optimal cytoreduction was achieved in 10 of the 15 cases (67%). The median PFS of the optimal cytoreduction patients was 14 months; on the other hand, that of the suboptimal cases was only 1 month ($P = 0.0003$ by log-rank test). The median OS of the optimal cytoreduction patients was 43 months, whereas that of the suboptimal cytoreduction cases was only 6 months, indicating that the prognosis of good cytoreduction patients was significantly better than that of suboptimal cytoreduction cases ($P = 0.0007$ by log-rank test) (Fig. 1). The optimal cytoreduction cases, with residual lesions ≤1 cm, also exhibited significantly better PFS and OS than did suboptimal cytoreduction cases ($P = 0.0005$ and 0.0029, respectively, by log-rank test, data not shown).

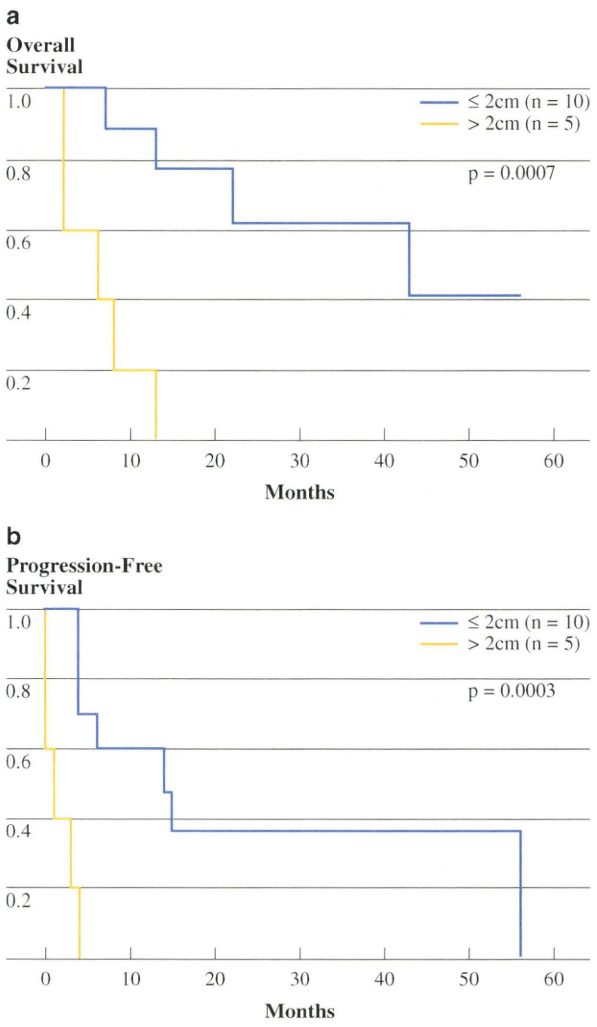

FIG. 1 **a** OS and **b** PFS of stage IVb endometrial cancer with intra-abdominal metastasis alone (group I). The median OS of the patients whose disease was cytoreduced to residual lesions ≤2 cm was 19 months, and that of the patients with residual lesions >2 cm after surgery was 6 months, exhibiting a statistically significant difference ($P = 0.0007$ by log-rank test). The median PFS of the patients whose disease was cytoreduced to residual lesions ≤2 cm was 10 months, and that of the patients with residual lesions >2 cm after surgery was 1 month, exhibiting a statistically significant difference ($P = 0.0003$ by log-rank test)

Effect of Cytoreductive Surgery for Stage IVb Endometrial Cancers with Extra-abdominal Metastasis (Group E)

Among the 18 stage IVb patients with extra-abdominal metastasis (group D), debulking surgery was conducted in 15 cases. Only palliative care was provided in the other three cases. Among the 15 cases in which debulking surgery was performed, good cytoreduction was achieved in 10 cases (67%), and of these 10, optimal cytoreduction was achieved in only 5 cases (33%). The median PFS of the

optimal cytoreduction patients was 24 months, and for suboptimal cytoreduction patients the mean PFS was only 3 months ($P = 0.013$ by log-rank test).

The median OS of the patients of optimal versus suboptimal cytoreduction was longer than 57 and 6 months, respectively. Because only 50% of patients with optimal cytoreduction died of endometrial cancer, an exact evaluation of the median OS based on the Kaplan–Meier method was not obtained. The median OS of optimal cytoreduction patients was statistically better than that of suboptimally cytoreduced patients ($P = 0.016$ by log-rank test) (Fig. 2). Significant complications from the surgical removal of extra-abdominally metastatic lesions were not detected.

Multivariate Cox Proportional-Hazards Analysis for Stage IVb Endometrial Cancers

We utilized a multivariate Cox proportional-hazards model in order to find evidence to further support our belief that, the larger the diameter of residual masses after cytoreductive surgery, the worse the prognosis of stage IVb endometrial carcinoma. The maximum size of residual lesions was demonstrated to be an independent factor for prognosis in group I (Table 5) and group E (Table 6). The adjusted hazard ratio (HR) for the maximum size of residual disease (>2 vs. ≤2 cm, i.e., optimal versus suboptimal) was 10.4 (95% CI, 1.27–84.70, $P = 0.030$) in group I and 16.92 (95% CI, 1.41–203.09, $P = 0.026$) in group E. In group I, the adjusted HR of the maximum size of residual disease (>1 vs. ≤1 cm, i.e., optimal vs. good) was 22.45 (95% CI, 1.43–353.54, $P = 0.028$, data not shown).

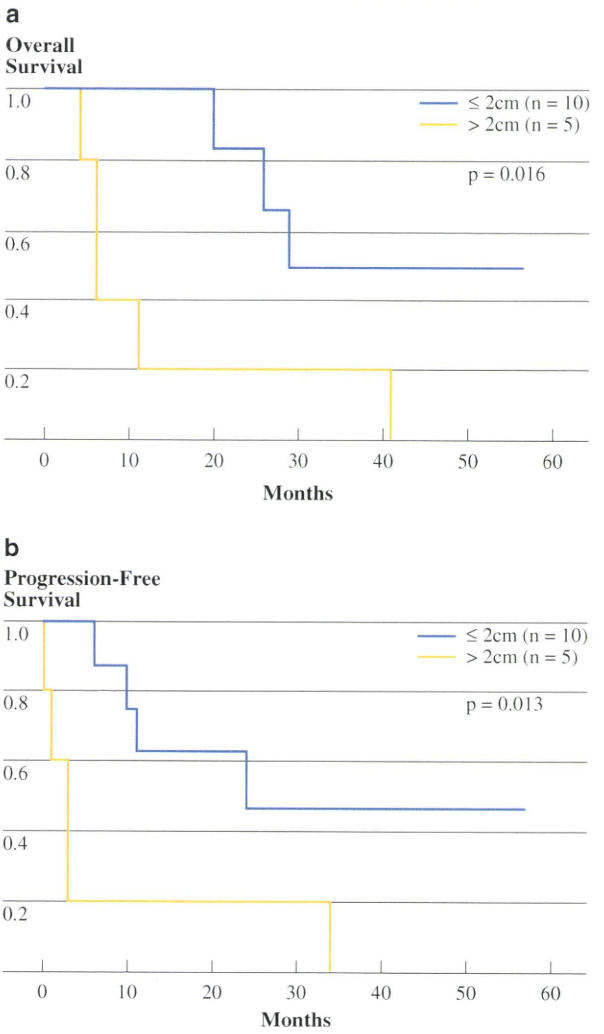

FIG. 2 **a** OS and **b** PFS of stage IVb endometrial cancer with extra-abdominal metastasis alone (group E). The median OS of the patients whose disease was cytoreduced to residual lesions ≤2 cm was 23 months, and that of the patients with residual lesions >2 cm after surgery was 6 months, exhibiting statistically significant difference ($P = 0.0016$ by log-rank test). The median PFS of the patients whose disease was cytoreduced to residual lesions ≤2 cm was 11.5 months, and that of the patients with residual lesions >2 cm after surgery was 3 months, exhibiting statistically significant difference ($P = 0.0013$ by log-rank test)

DISCUSSION

We have investigated various clinicopathological factors related to the prognosis of stage IVb endometrial cancer. The oldest patients were shown to have the worst prognosis, consistent with a previous report.[2] On the other hand, the histological type of the tumor, the distribution of the disease, and the regimen of postoperative chemotherapy were not related to patient prognosis. This is, perhaps, because of the small sample size. In our study, the endometrioid type of tumor demonstrated better prognosis compared with the serous and clear cell types; however, this tendency was not statistically significant, also consistent with Bristow et al.'s study.

Maximal cytoreduction of ovarian tumors was previously demonstrated to be one of the most powerful determinants of survival among ovarian cancer patients.[6,7] The beneficial effect of cytoreductive surgery was further assisted by the ovarian tumors' high sensitivity to postoperative chemotherapy using platinum and taxanes. Recently, the effectiveness of similar chemotherapy for advanced endometrial cancer cases, using platinum and taxanes, with or without adriamycin, and a possible role of cytoreductive surgery were demonstrated.[2,8,9,11–13] Bristow et al. showed that, when optimal cytoreduction (residual disease ≤1 cm) was achieved in 36 out of 65 (55%) cases, the median OS of optimally versus suboptimally cytoreduced patients was 34.3 and 11.0 months, respectively ($P = 0.0001$ by log-rank test). Ayhan et al. demonstrated that, when optimal cytoreduction was achieved in 22 out of 37 (60%) cases, the median OS of optimally versus suboptimally cytoreduced patients was 25 and 10 months, respectively ($P = 0.001$ by

TABLE 5 Multivariate Cox proportional-hazards analysis for stage IVb endometrial cancer with intra-abdominal metastasis alone (group I)

Variable	Adjusted HR	95% CI	*P*-value
Age (years)			0.84
<70	1		
≥70	0.785	0.07–8.26	
Histology			0.95
Endometrioid	1		
Serous, clear	1.07	0.14–8.37	
Number of regions with metastasis			0.66
≤2 regions	1		
≥3 regions	1.67	0.17–16.11	
Maximum size of residual tumors			0.030
>2 cm	1		
≤2 cm	10.4	1.27–84.70	
Postoperative chemotherapy			0.20
TEC, TC	1		
Others	3.26	0.53–20.13	

The adjusted hazard ratio (HR) of maximal size of residual disease >2 cm compared with maximal size of residual disease ≤2 cm was 10.4 (95% CI, 1.27–84.70, $P = 0.030$)

TEC or TC: paclitaxel and carboplatin, with or without epirubicin

TABLE 6 Multivariate Cox proportional-hazards analysis for stage IVb endometrial cancer with extra-abdominal metastasis (group E)

Variable	Adjusted HR	95% CI	*P*-value
Age (years)			0.20
<70	1		
≥70	6.86	0.37–126.12	
Histology			0.77
Endometrioid	1		
Serous, clear	0.58	0.02–21.40	
Number of regions with metastasis			0.17
≤2 regions	1		
≥3 regions	1.16	0.52–47.60	
Maximum size of residual tumor			0.026
≤2 cm	1		
>2 cm	16.92	1.41–203.09	
Postoperative chemotherapy			0.47
TEC, TC	1		
Others	3.20	0.14–73.09	

The adjusted hazard ratio (HR) of maximal size of residual disease >2 cm compared with maximal size of residual disease ≤2 cm was 16.92 (95% CI, 1.41–203.09, $P = 0.026$)

TEC or TC: paclitaxel and carboplatin, with or without epirubicin

log-rank test). Chi et al. showed that, when good cytoreduction (to ≤2 cm) was achieved in 24 out of 45 (53%) cases, the median OS of good and suboptimal cytoreduction patients was 31 and 12 months, respectively.

However, the role of debulking surgery in advanced endometrial cancer with extra-abdominal metastasis was unclear, primarily because the stage IVb cases analyzed in the above studies had only intra-abdominal metastasis. In our present study, we found that the extent of cytoreduction strongly contributed to the prognosis of stage IVb endometrial cancer patients. Moreover, the effectiveness of cytoreductive surgery in terms of survival was demonstrated in cases with intra-abdominal metastasized lesions alone (group I) and, for the first time, in those with extra-abdominal metastasis (group E). The median PFS and OS of group E were almost equal to those of group I.

The prognosis of our cases was slightly better than those of previous reports, which found a median OS of 19–51 months (Table 7).[2,8,9,14–17] This tendency may be due to a lower frequency of non-endometrioid-type tumors in our population group, or to the higher rate of optimal cytoreduction, or to the frequent use of postoperative TEC chemotherapy. Surprisingly, the best cytoreduction indicated in our present study was when the residual mass was ≤2 cm, not ≤1 cm.

Lambrou et al. showed that OS was lower and morbidity was higher in patients with advanced endometrial cancer (mainly stage III).[18] They suggested that alternative treatment options should be considered in patients with surgically unresectable disease. However, our study provides clear evidence that optimal cytoreduction significantly improves the prognosis of stage IVb endometrial cancer with only intra-abdominal metastases. For the first time, we show that surgical cytoreduction that leaves only tumors ≤2 cm can play a critical role in those advanced cases with extra-abdominal metastasis. Our findings indicate that cytoreduction should be considered for all stage IVb endometrial cancers whose primary tumors are resectable, even those with extra-abdominal metastasis.

There are, unfortunately, limitations to our study. Firstly, the study was retrospective, thus there might be unintended biases. Secondly, the number of patients (33) was not sufficient to provide definitive results, despite the statistical analysis performed. The association of the pre-surgical size of the metastatic lesions and the rate of achievement of optimal cytoreduction and prognosis was not evaluated. Moreover, as Chi et al. described in their previous report, it is still unclear whether improved survival in optimally cytoreduced patients is due to the surgical resection itself, or instead is due to the presence of less aggressive disease in these patients that allowed for the surgery.[9] However, in our study, the maximum size of residual lesions was demonstrated to be more significant for survival than the number of metastatic regions.

TABLE 7 Previous reports of cytoreductive surgery for stage IV endometrial cancel

Author (year)	Cases	Non-endometrioid[a]	Stage	Cytoreduction	Optimal rate	Median OS (months)[b]
Goff (1994)[14]	47	40%	IV	Ope or no	–	19
Chi (1997)[9]	55	49%	IV	2 cm	53%	31 (mean)
Bristow (2000)[2]	65	65%	IVb	1 cm	55%	34
Bristow (2001)[15]	31	100% (serous)	IV	1 cm	52%	26
Ayhan (2002)[8]	37	21%	IVB	1 cm	60%	25
Meinnrzadeh (2002)[16]	35	100% (serous)	IIIc/IV[c]	Microscopic	57%	40
Thomas (200)[17]	70	100% (serous)	IIIc/IV[c]	1 cm	60%	14
				Microscopic	37%	51
This study (2009)	33	27%	IVb (intra/extra)[d]	2 cm	67%	43
					(67%/67%)	(43/>57)

[a] Proportion of non-endometrioid histological type

[b] Median OS of the cases in which operation was performed in Goff et al.'s report and that of the cases in which optimal cytoreduction was performed in the other reports

[c] In Memarzadeh's study, 16 cases were stage IIIc, 2 cases were stage IVa, and 17 cases were stage IVb; in Thomas's study, 12 cases were stage IIIc and 58 cases were stage IV

[d] Cases with intra-abdominal metastasis alone (group I)/cases with extra-abdominal metastasis (group E)

Further investigation is still required to establish an effective standard therapy for stage IVb endometrial cancer; however, our study, for the first time, provides a rationale for conducting aggressive cytoreductive surgery for endometrial carcinoma with extra-abdominal metastasis.

ACKNOWLEDGMENT The authors would like to thank G. S. Buzard, CDCP, Michele Buzard, Kaplan University-Hagerstown, and Jonathan Mitchell, Virginia Technical University, for their constructive critiques and editing of our manuscript.

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Original Article

Gynecologic and Obstetric Investigation

Gynecol Obstet Invest 2010;69:224–232
DOI: 10.1159/000273207

Received: March 26, 2009
Accepted after revision: October 27, 2009
Published online: January 7, 2010

Concurrent Weekly Nedaplatin, External Beam Radiotherapy and High-Dose-Rate Brachytherapy in Patients with FIGO Stage IIIb Cervical Cancer: A Comparison with a Cohort Treated by Radiotherapy Alone

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Key Words

Chemoradiotherapy · Stage IIIb cervical cancer, recurrence · Nedaplatin · High-dose-rate intracavitary brachytherapy

Abstract

Objectives: The aim of this study was to evaluate whether nedaplatin-based concurrent chemoradiotherapy (CCRT) using high-dose-rate intracavitary brachytherapy (HDR-ICBT) is superior to radiotherapy (RT) alone in patients with FIGO stage IIIb cervical cancer. ***Methods:*** The records of 41 consecutive women treated either with nedaplatin-based CCRT using HDR-ICBT (n = 20) or RT alone (nonrandomized control group, n = 21) for stage IIIb cervical cancer were retrospectively reviewed. The activity and toxicity were compared between the two treatment groups. Progression-free survival (PFS) and overall survival (OS) were the main endpoints. ***Results:*** The 5-year overall survival rates in the CCRT and RT groups were 65 and 33.3%, respectively. The median OS of the CCRT and RT groups were 60 and 29 months, respectively. CCRT was significantly superior to RT alone with regard to PFS (p = 0.0015) and OS (p = 0.0364). The frequency of acute grade 3–4 toxicity was significantly higher in the CCRT group than in the RT group. However, no statistically significant difference was observed with regard to severe late toxicity. ***Conclusions:*** Nedaplatin-based concurrent chemoradiotherapy was safely performed and significantly improved the prognosis of patients with FIGO stage IIIb cervical cancer. This treatment can be considered as an alternative to cisplatin-based chemoradiotherapy in this patient population.

Introduction

Radiotherapy (RT) is the major treatment modality for invasive cervical cancer and has achieved significant treatment outcomes; however, substantial treatment failure still occurs, especially in advanced-stage patients [1].

The treatment of FIGO stage IIIb cervical cancer is challenging and poses special problems. Investigators have reported a survival rate of between 30 and 50% for stage IIIb cervical cancer patients with RT alone [2].

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One of the major clinical limitations in the management of stage IIIb disease is the size of the tumor. The tumor volume in patients with stage IIIb disease is usually large. It is generally accepted that the ability of RT to cure locally advanced cervical cancer is limited by the size of the tumor because the dose required to treat a large tumor exceeds the limit of toxicity in normal tissue [3]. Therefore, efforts to maximize local control and eventually improve survival and the quality of life of these patients are necessary.

For this purpose, various clinical studies have evaluated the survival benefit of adding concurrent chemotherapy. When added to RT, cisplatin was demonstrated to reduce the risk of death from cervical cancer by approximately 50% [4–7]; however, its results are far from optimal in patients with stage III or greater disease. According to a recent update from the Radiation Therapy Oncology Group protocol 90-01, the 5-year survival rate of patients with stage Ib–IIa treated with a combination of chemotherapy and RT is 78%, compared to 59% in patients with stage III–IVa disease [8]. Therefore, other therapeutic approaches must be tested in order to further improve outcomes.

An important problem in the management of patients with stage IIIb cervical cancer is the presence of hydronephrosis as a result of ureteral obstruction due to parametrial disease involvement. It has previously been reported that the presence of hydronephrosis is an important indicator of poor prognosis [9]. The precise incidence of ureteral obstruction is unknown, but it is reported to be 7% among all cases of invasive cervical cancer and 55.8% among patients with stage III–IV disease [9]. Although weekly cisplatin during RT has been reported to be well tolerated, its nephrotoxicity may limit the use of this agent for stage IIIb cervical cancer patients, especially in patients with impaired renal function due to ureteral obstruction. Therefore, the use of an agent that shows less nephrotoxicity as a radiosensitizer may improve the outcome of these patients.

Nedaplatin (*cis*-diammine-glycoplatinum), a derivative of cisplatin, was developed by Shionogi Pharmaceutical Co. in Japan, with the aim of producing a treatment with lower renal and gastrointestinal toxicity but effectiveness similar to cisplatin.

In a preclinical evaluation of its effectiveness against cervical cancer, nedaplatin demonstrated significant antitumor activity similar to cisplatin [10, 11]. Its lower incidence of nephrotoxicity in comparison to cisplatin was demonstrated to be associated with a difference in the kidney distribution of these drugs. When the two agents were administered at the same dose, the accumulation of nedaplatin in the kidney was approximately 40% of that of cisplatin, leading to the lower nephrotoxicity of nedaplatin [12, 13].

Clinically, previous phase II studies conducted in Japan suggested that nedaplatin has particularly strong clinical efficacy on squamous cell carcinoma of the head and neck, esophagus and uterine cervix [14, 15]. In a phase II clinical trial, nedaplatin demonstrated a response rate of 46% in patients with recurrent cervical cancer, which was slightly superior to that obtained with cisplatin (39%) [16]. On the basis of the results of these phase II studies, although there have been no controlled clinical trials demonstrating the equivalency of these agents, nedaplatin has been used clinically in Japan as an alternative to cisplatin for patients with recurrent cervical cancer [17].

The radiosensitizing properties of nedaplatin have been demonstrated in several preclinical studies [18, 19], and preliminary data from clinical studies of nedaplatin-based concurrent chemoradiotherapy (CCRT) in patients with head and neck, esophageal or uterine cervical cancer have been reported [20–22]. However, the clinical experience with the use of this agent in the setting of CCRT in patients with cervical cancer is limited. Since nedaplatin exhibits minimal nephrotoxicity, it can be used in patients with marginal renal function [23, 24]. Moreover, since nedaplatin does not require hydration, it is manageable in an outpatient setting. Thus, the substitution of nedaplatin for cisplatin as a concurrent chemotherapy in patients with stage IIIb cervical cancer may be beneficial.

In addition to employing a more effective treatment strategy to improve survival, it is also important to maintain a patient's quality of life. High-dose-rate intracavitary brachytherapy (HDR-ICBT) has several advantages over low-dose-rate (LDR)-ICBT such as its short treatment time and can therefore be administered on an outpatient basis. In Japan, approximately 90% of patients with invasive cervical cancer are treated using HDR-ICBT [25]. HDR-ICBT has demonstrated local control, survival and morbidity comparable to LDR-ICBT with acceptable complications in patients with cervical cancer [26–28]. However, it is not clear if it is safe or effective to give chemotherapy concurrently with external beam RT (EBRT) and HDR-ICBT as very few published series have examined its benefit and toxicity.

Based on the US National Cancer Institute alert in 1999 and a clinical trial in our institution showing a comparable local control rate with acceptable toxicity be-

tween LDR- and HDR-ICBT [26], we have started the clinical use of nedaplatin-based CCRT using HDR-ICBT to determine if concurrent nedaplatin is a suitable alternative to cisplatin in patients with cervical cancer.

In the current study, we conducted a retrospective analysis to evaluate whether nedaplatin-based CCRT is safe and superior to RT alone in Japanese patients with FIGO stage IIIb cervical cancer.

Materials and Methods

Patients

Permission to proceed with data acquisition and analysis was obtained from the Osaka University Hospital's institutional review board. A list of patients with FIGO stage IIIb cervical cancer who had been treated with CCRT using HDR-ICBT from 1999 to 2004 at Osaka University Hospital was generated from our institutional tumor registry information. Then, through a chart review, their clinical data were retrospectively reviewed.

All patients had primary, previously untreated and histologically confirmed carcinoma of the uterine cervix. The pretreatment workup consisted of a complete medical history and physical examination, complete blood count, biochemistry panels, chest X-ray and computed tomography (CT) of the abdomen and pelvis, magnetic resonance imaging (MRI) and optional intravenous pyelography, cystoscopy and rectosigmoidoscopy. Lymph nodes measuring 10 mm or more along their longest axis on CT or MRI were defined as metastatic nodes.

Patients were staged clinically according to the International Federation of Gynecology and Obstetrics staging criteria by both a gynecological oncologist and a radiation oncologist without general anesthesia. Patients with unfavorable geometry in which the target volume could not be adequately covered by an intracavitary source and who were therefore treated using interstitial brachytherapy were excluded. Patients who received extended-field RT were also excluded. Patients with radiologic evidence of positive pelvic lymph nodes were eligible, but those with radiologic evidence of para-aortic disease were excluded. No patient underwent a lymph node biopsy to confirm the radiologic findings.

MRI was used to evaluate the size and geometry of the primary tumor. The maximal tumor diameter was measured three-dimensionally based on T_2-weighted images. The longest diameter was considered valid as the maximal tumor diameter.

Radiotherapy

The radiotherapy consisted of EBRT followed by HDR-ICBT. The EBRT was performed using a 10-MV X-ray machine. Using anteroposterior parallel opposed portals, the external irradiation was delivered to the whole pelvis at 2 Gy/fraction for 5 fractions/week, for a total of 25 fractions (50 Gy). The superior margin of the external radiation field was placed on the upper border of the fifth lumbar vertebra, and the inferior margin was the inferior border of the obturator foramen but was extended inferiorly when there was vaginal invasion. Laterally, the field extended 1.5–2 cm beyond the lateral margin of the bony pelvic wall. A midline block (4 cm width at the midline) was inserted into the central lower two-thirds length of the pelvic field after 30 Gy had been delivered. After adequate tumor regression, the HDR-ICBT was performed once a week during the course of the EBRT with the centrally shielded field. Usually, the first HDR-ICBT was applied after 30 Gy of EBRT. ICBT was administered to the patients using a Microselectron HDR (Nucletron, Veenendaal, The Netherlands). A set of Fletcher-type metal applicators (Nucletron) was mainly used for ICBT. For patients with vaginal infiltration or with a narrow vagina, a tandem with a vaginal cylinder was used. Vaginal packing was used to maximize the distance from the source to the bladder wall and the rectal wall. The ICBT dose was delivered to point A, which was defined as 2 cm above the cervical os marker and 2 cm perpendicular to the uterine axis along the plane of the uterus. The planned total dose of HDR-ICBT was 27.2 Gy in 4 fractions. No EBRT was performed on the same day as HDR-ICBT.

Chemotherapy

Chemotherapy was given intravenously with nedaplatin weekly during the course of EBRT and HDR-ICBT for 5 weeks. Nedaplatin was not administered on the same day as ICBT. The median number of cycles per patient was 5 (range: 2–5), and the median dose of nedaplatin was 35 mg/m^2 (range: 10–45). The first cycle of nedaplatin was initiated on the first treatment day of RT. The drug was given in a 1-hour infusion. Renal function and blood counts were assessed before each cycle. Nedaplatin administration was suspended when the granulocyte count was less than 1,500/μl or the platelet count was less than 100,000/μl. Nedaplatin administration was also suspended if the patient could not tolerate the acute gastrointestinal toxicity during the course of the treatment. During the weeks in which the patient did not receive chemotherapy, radiation was continued as long as the white blood cell count was more than 2,000/μl and the platelet count was more than 50,000/μl.

Control Patients

A nonrandomized control group of patients with stage IIIb cervical cancer who had been treated with definitive RT alone from 1997 to 2004 were also identified through the chart review and served as a control. RT for these patients consisted of a combination of EBRT (50 Gy to the whole pelvis) and HDR-ICBT (27.2 Gy to point A), which was the same as the treatment for the patients treated with CCRT.

Toxicity

Clinical data regarding treatment-related complications were also collected. Complications that occurred within 90 days from the start of the primary treatment were considered to be acute complications, and those that occurred more than 90 days after the start of treatment were considered as late complications. The severity of acute complications was classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 2.0. Late complications were graded according to the Radiation Therapy Oncology Group Late Radiation Morbidity Scoring Scheme [29].

Follow-Up

Patients were followed regularly and observed for acute and late toxicity by both gynecological oncologists and radiation on-

cologists. During the treatment, the patients were evaluated weekly by pelvic examination and complete blood count. For patients treated with chemoradiation, renal and liver function tests were also performed weekly. MRI examinations were performed at 30–40 Gy of EBRT to assess their response to treatment and the applicability of ICBT. After the end of the treatment, the patients were followed up in an outpatient clinic every month in the first year, every 2 months in the second year, every 3 months in the third year, every 6 months in the fourth to fifth years, and annually thereafter. Pelvic failure was defined as disease persisting or recurring in the pelvis, including central and parametrial failure. Distant failure was defined as disease occurring outside the pelvis, including the para-aortic lymph nodes. When local recurrence was suspected by pelvic examination or smears, a biopsy was taken for confirmation whenever possible. Patients who showed evidence of progressive pelvic abnormality on physical examination or who had the clinical triad of sciatic pain, hydronephrosis and leg edema with radiologic evidence of recurrence were considered to have pelvic recurrence even without histologic documentation. No patient was lost to follow-up. The median duration of the follow-up was 60 months (range: 1–109 months).

Statistical Analysis

The differences between the groups with respect to stage, histology, node status, pelvic node fixation, involvement of the lower third of the vagina, the presence of hydronephrosis, the site of recurrence and treatment-related toxicity were assessed using Fisher's exact test. The maximum tumor diameter and pretreatment hemoglobin level were compared using Welch's t test. The survival analysis was based on the Kaplan-Meier method and was compared by the log-rank test. Progression-free survival (PFS) was defined as the time from the date of primary diagnosis to the date of the first physical or radiographic evidence of disease progression, death or the last follow-up visit. Overall survival (OS) was defined as the time from the date of the primary diagnosis to the date of death or the last follow-up visit. p values <0.05 were considered statistically significant.

Results

Patient Characteristics

Forty-one consecutive women with FIGO stage IIIb cervical cancer who were treated with nedaplatin-based CCRT (n = 20) or RT alone (n = 21) were identified. The clinicopathologic characteristics of these patients are shown in table 1. All women had squamous cell carcinoma. Most patients had massive tumors with a median tumor diameter of 6.2 cm. Although hydronephrosis was observed in a total of 13 patients, none of these had renal dysfunction with an elevated serum creatinine or blood urea nitrogen level. The characteristics of the patients in the RT group were similar to those in the CCRT group (table 1). There were no significant differences in patient characteristics except for age.

Table 1. Patient characteristics

	CCRT group (n = 20)	RT group (n = 21)	p value
Median age, years	59	67	0.0122
Histology			
SCC	20	21	1.00
Others	0	0	
Mean maximal tumor diameter, mm	61.6	59.6	0.7723
Mean pretreatment hemoglobin level, mg/dl	11.9	11.0	0.2138
Pelvic node status			
Positive	11	9	0.5377
Negative	9	12	
Pelvic wall fixation			
Bilateral	3	5	0.6965
Unilateral	17	16	
None	0	0	
Lower third of vagina			
Not involved	20	19	0.4878
Involved	0	2	
Hydronephrosis			
Bilateral	0	1	0.2369
Unilateral	4	8	
None	16	12	

SCC = Squamous cell carcinoma.

Table 2. Treatments and survival

	CCRT group (n = 20)	RT group (n = 21)	p value
Dose of nedaplatin administered, mg/m^2			
Median	35	–	
Range	10–45		
Courses of nedaplatin administered			
Median	5	–	
Range	2–5		
Duration of RT, days			
Median	45	47	0.8723
Range	40–57	41–61	
PFS, months			
Median	60	7	0.0015
Range	0–60	0–60	
Mean	43.3	21.4	
OS, months			
Median	60	29	0.0364
Range	5–60	1–60	
Mean	47	32.2	

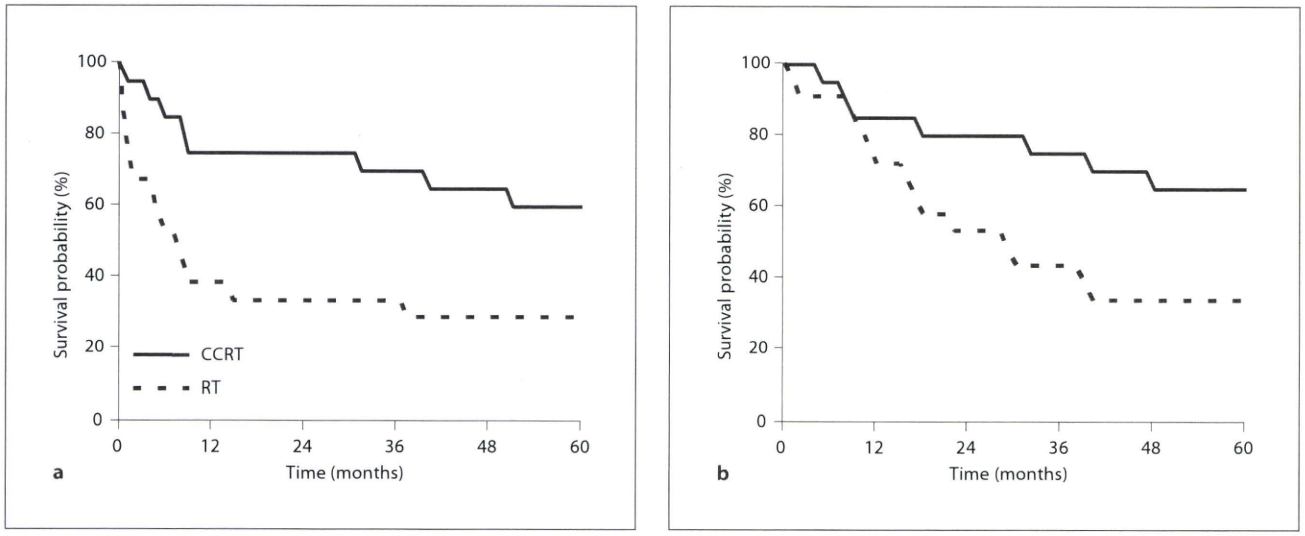

Fig. 1. a PFS among patients in the CCRT group and RT group. **b** OS among patients in the CCRT group and RT group.

Treatment Outcome

As shown in table 2, among the patients treated with CCRT, the median dose of nedaplatin administered was 35 mg/m^2 (range: 10–45), and the median course number of nedaplatin administered was 5 (range: 2–5). The median and mean PFS were 60 and 43.3 months, respectively. The median and mean OS were 60 and 47 months, respectively. The 5-year OS rate was 65% in patients treated with CCRT. On the other hand, in the RT group, the median and mean PFS were 7 and 21.4 months, respectively. The median and mean OS were 29 and 32.2 months, respectively (table 2). The 5-year OS rate was 33.3%, which was similar to the results from previous reports, which showed a response rate of 30–50% [2]. When the CCRT group was compared with the RT group, as shown in figure 1 and table 2, CCRT was significantly superior in terms of PFS (log rank; $p = 0.0015$) and OS (log rank; $p = 0.0364$). These results indicate that the addition of concurrent nedaplatin to pelvic EBRT plus HDR-ICBT significantly improved the prognosis in this patient population.

As shown in table 3, treatment failure was observed in 7 patients (35%) in the CCRT group and in 14 patients (66.7%) in the RT group. Among the 7 patients with treatment failures in the CCRT group, the first site of relapse was pelvic in 4, 2 showed synchronous pelvic and distant relapse sites, and 1 patient developed distant relapse. All pelvic failures involved uterine recurrence. In the RT group, among the 14 patients with treatment failure, the first site of relapse was pelvic in 6, 5 showed synchronous pelvic and distant relapse sites, and 3 patients developed distant relapse. The rate of treatment failure was higher in the RT group than in the CCRT group; however, the difference was not statistically significant ($p = 0.0629$). The pattern of failure was not different between the two groups ($p = 0.2686$).

Adverse Effects

Generally, nedaplatin-based CCRT was well tolerated. Among the patients in the CCRT group, the most frequently observed acute toxicity was hematologic. As shown in table 4, grade 3 or 4 acute toxicity was observed in 10 patients (50%) in the CCRT group. Among these patients, 7 had grade 3–4 neutropenia alone, and 3 had both grade 3–4 neutropenia and thrombocytopenia. All of these resolved without requiring colony-simulating growth factor or platelet transfusions. Although grade 1–2 acute nonhematologic toxicities such as gastrointestinal toxicity were commonly observed, there were no grade 3–4 nonhematologic toxicities.

In the RT group, although grade 1–2 acute toxicities such as hematologic or gastrointestinal toxicity were commonly observed, grade 3 or 4 toxicities were only observed in 1 patient (5%). This patient suffered from bowel obstruction and was cured by conservative treatment without requiring an ileus tube or a surgical inter-

Table 3. Patterns of failure

	CCRT group (n = 20)		RT group (n = 21)	
	patients, n	site of relapse	patients, n	site of relapse
Pelvic	4	4: uterus	6	5: uterus 1: pelvic side wall
Pelvic + distant	2	1: uterus, PALN, SCLN 1: uterus, liver, lung, dissem.	5	2: uterus, bone 2: uterus, PALN 1: uterus, liver, PALN, dissem.
Distant	1	1: PALN	3	1: lung 1: lung, bone 1: PALN
Total with recurrence	7 (35%)		14 (66.7%)	

PALN = Para-aortic lymph node; SCLN = supraclavicular lymph node; dissem. = peritoneal dissemination.

Table 4. Acute toxicity (grade 3–4)

	CCRT group (n = 20)	RT group (n = 21)	p value
Hematologic			
Neutropenia	7	0	
Thrombocytopenia	0	0	
Neutropenia + thrombocytopenia	3	0	
Nonhematologic			
Gastrointestinal	0	1	
Genitourinary	0	0	
Total number of patients with grade 3–4 acute toxicity	10 (50%)	1 (4.8%)	0.0014

vention. The incidence of grade 3–4 acute toxicity was significantly higher in the CCRT group than in the RT group.

Grade 3–4 severe late toxicities were observed in 2 patients (10%) who had been treated with CCRT. Of these, 1 patient developed a rectovaginal fistula 15 months after the completion of CCRT. The other patient, whose death was attributed to treatment, developed a rectal perforation and died as a result of peritonitis and septicemia 40 months after completing the treatment. While the absolute number of late toxic events was increased with the nedaplatin-based CCRT, the difference was not statistically significant. Moreover, there were no significant differences in the length of RT among these treatment groups (table 2).

Discussion

Of the previous randomized studies that examined the benefits of cisplatin-based CCRT in patients with invasive cervical cancer [4–7, 30] only one study, which showed a negative result, allowed the use of HDR, medium-dose or LDR-ICBT. In this report, however, only 15% of patients were treated with HDR-ICBT [30]. Therefore, it remains unanswered whether the addition of concurrent chemotherapy to HDR-ICBT is safe and is also better than RT alone.

In the current study, nedaplatin-based CCRT was well tolerated. All patients completed the planned EBRT and HDR-ICBT. The optimal dose of concurrent weekly nedaplatin in patients with invasive cervical cancer treated by primary CCRT using EBRT and HDR-ICBT is still un-

Table 5. Literature review: survival, treatment failure and complications

Authors	Year	Study type	Concurrent chemotherapy	Brachy-therapy	Stage	Follow-up years	OS %	Treatment failure %	Late toxicity (grade 3–4) %
Teshima et al. [26]	1993	RCT	–	HDR	III	5	53	47	10
Hareyama et al. [27]	2002	RCT	–	HDR	III	5	69	49	7
Lertsanguansinchai et al. [28]	2004	RCT	–	HDR	IIIb	3	71	30	7
Morris et al. [5]	1999	RCT	cisplatin	LDR	III–IVa	5	63	42	12
Rose et al. [6]	1999	RCT	cisplatin	LDR	II–IVa	4	66	38	1.7
Toita et al. [33]	2005	retro.	cisplatin	HDR	I–III	3	79	33	2
Chung et al. [34]	2005	phase I/II	cisplatin	HDR	IIb–IVa	3	83	19	6
Chen et al. [35]	2006	retro.	cisplatin	HDR	IIb–III	4	74	46	14
Pötter et al. [36]	2006	retro.	cisplatin	HDR	Ib–IVa	3	61	44	4
Novetsky et al. [37]	2007	retro.	cisplatin	HDR	III–IV	5	65	35	6
Current study	2009	retro.	nedaplatin	HDR	IIIb	5	65	35	10

RCT = Randomized controlled study; retro. = retrospective study; HDR = high-dose rate; LDR = low-dose rate.

known but has been investigated in several clinical studies [21, 22, 31, 32]. Of these, two studies recommended 30 mg/m^2 nedaplatin for 5 weeks, and another two recommended 30 or 35 mg/m^2 nedaplatin for 6 weeks as a standard treatment regimen. Therefore, the dose of nedaplatin used in the current study was consistent with these previous studies.

Since only a few small series have been published that describe CCRT with HDR-ICBT [33–37], it is difficult to estimate the precise incidence of complications. In the current study, grade 3–4 acute toxicities were observed in 50% of patients, which was similar to the findings of a recent phase II study of nedaplatin-based chemoradiotherapy [22]. Nevertheless, there were no significant differences in the length of RT among these treatment groups. The frequencies of acute grade 3–4 toxicities were significantly higher in the CCRT group than in the RT group. This finding is consistent with previous studies that showed that the acute adverse effects were increased with CCRT [4–7].

With regard to RT using EBRT and LDR-ICBT, late toxicity from concurrent chemotherapy had been examined previously, and no differences were found in the rates of bowel or bladder toxicity between patients treated with RT alone and those treated with CCRT [38]. However, because of the lack of a controlled clinical study, it is not clear whether concurrent chemotherapy increases the incidence of late toxicity in the setting of RT using EBRT and HDR-ICBT. In our study, severe late complications were observed in the patients treated with CCRT. As shown in table 5, the rate of severe late complications in the CCRT group in our study (10%) was similar to those of other series in which the patients had been treated with EBRT and HDR-ICBT without CCRT [26–28] or with cisplatin-based CCRT using EBRT and LDR-ICBT [5, 6]. These results including ours suggest that the addition of concurrent weekly nedaplatin to EBRT and HDR-ICBT does not increase late toxicity.

Our retrospective study demonstrated significant improvements in PFS and OS in patients treated with CCRT. The risk of death was decreased by 46% by the addition of nedaplatin-based concurrent chemotherapy. The 5-year overall survival rate of 65% and the treatment failure rate of 35% in our study are comparable to those found by previous clinical studies of cisplatin-based CCRT (table 5). These results suggest that nedaplatin can be considered as an alternative to cisplatin in the setting of chemoradiotherapy in this patient population.

It has been reported that pelvic recurrence is a major cause of treatment failure in patients with FIGO stage IIIb cervical cancer [3, 4, 26]. Our results also confirmed that pelvic recurrences continue to be the major cause of mortality, despite aggressive treatment with CCRT (table 3).

Of a total of 20 patients treated with CCRT, 10 did not receive optimal planned doses and cycles of concurrent chemotherapy. However, only 2 of these patients developed recurrences. In contrast, of a total of 10 patients who received optimal treatment, 5 developed recurrences, indicating that treatment failure was not common in pa-

tients who could not receive the assigned dose of chemotherapy.

To further improve the local control rate, novel treatment strategies such as the use of new cytotoxic agents as concurrent chemotherapies, the use of biologic agents as radiosensitizers or more conformal dose distributions with intensity-modulated RT need to be investigated in future clinical trials.

In conclusion, our data demonstrate that the concurrent use of weekly nedaplatin with EBRT and HDR-ICBT significantly improved the prognosis of patients with FIGO stage IIIb cervical cancer. This study should be interpreted cautiously for several reasons, such as its retrospective design, the relatively small cohort of patients and the heterogeneity of the patient population. However, we believe that our encouraging results are sufficient to warrant further investigation of nedaplatin-based CCRT in a future randomized controlled trial in patients with FIGO stage IIIb cervical cancer.

Acknowledgements

We thank Remina Emoto for her secretarial assistance. This work was supported in part by a Grant-in-Aid for Young Scientists (No. 21791554) from the Ministry of Education, Culture, Sports, Science and Technology of Japan, and a Grant-in-Aid for General Scientific Research (No. 21390453).

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Int J Clin Oncol (2010) 15:77–81
DOI 10.1007/s10147-009-0014-4

ORIGINAL ARTICLE

Amputation of uterine corpus as the intraoperative modification during cesarean radical hysterectomy for invasive cervical cancer during pregnancy

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Received: 11 May 2009 / Accepted: 17 September 2009 / Published online: 19 January 2010

Abstract
Objective Cesarean radical hysterectomy (CRH) for invasive cervical cancer during pregnancy is characterized by heavy blood loss. Any surgical modifications made in an attempt to reduce the blood loss are valuable. Our study was designed to evaluate the efficacy of amputating the uterine corpus during CRH.
Methods All cases of radical hysterectomy (RH) were evaluated. Cases were divided into: (a) cesarean section immediately followed by RH for invasive cervical cancer complicating pregnancy (CRH group); and (b) RH for nonpregnant subjects (RH group). The information abstracted included estimated blood loss (EBL), operative time, intraoperative transfusion, and use of amputation of uterine corpus during CRH. Nonparametric tests were used for the statistical analysis.
Results There were five CRH cases (3 for CRH with amputation, 2 for CRH without amputation) and 209 RH cases were evaluated for statistics during the study period. The difference in mean operative time between the CRH group and the RH group was not statistically significant: 276.6 min (range 160–425) versus 297.3 min (range 147–645), $p = 0.66$. The mean EBL for the CRH group was significantly larger than that for the RH group: 2106.6 ml (range 730–4150) versus 858.8 ml (range 150–4770), $p < 0.001$. Mean operative time and mean EBL for CRH with amputation of uterine corpus were significantly less than those for CRH without amputation of uterine corpus: operative time, 186.0 min (range 160–228) versus 412.5 min (range 400–425), $p = 0.043$; EBL, 1034.3 ml (range 730–1540) versus 3715.0 ml (range 3280–4150), $p = 0.043$. No intraoperative tumor exposures were observed in the amputated cases.
Conclusion Amputation of uterine corpus during CRH for invasive cervical cancer during pregnancy significantly improves the intraoperative performance, although it should be used with care.

Keywords Cervical cancer · Pregnancy · Cesarean radical hysterectomy · Amputation of uterine corpus · Surgical complication

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Introduction

Cervical cancer is reported to occur during approximately one in 2200 pregnancies, and is the most common gynecologic malignancy that complicates pregnancy [1]. Three percent of cervical cancers are diagnosed during pregnancy [2]. The management of patients with early-stage cervical cancer during pregnancy is similar to that of nonpregnant patients, and radical surgery is the treatment of choice [2, 3]. Cesarean delivery is recommended as the mode of delivery for pregnant women with cervical cancer because

of the high recurrence rate of cervical cancer for women who deliver vaginally [4].

Cesarean section immediately followed by radical hysterectomy (RH), or cesarean radical hysterectomy (CRH), was first described in 1958 [5]. CRH has the benefit of incurring fewer complications than radiation therapy [6], but heavy blood loss during CRH is a major surgical complication [7, 8].

Our study was designed to see if there is a surgical modification that improves the intraoperative blood loss during CRH in order to reduce the risk of surgical complications.

Methods

This is a retrospective cohort study based on a registered operative record review focusing on Osaka Rosai Hospital and Osaka University Hospital, Osaka, Japan, between 1 January 2000 and 31 December 2005. Operative records of RH performed at Osaka Rosai Hospital and Osaka University Hospital during the study period were evaluated. The subjects who underwent CRH for cervical cancer complicating pregnancy were categorized as the CRH group. The subjects who underwent RH for nonpregnant women were categorized as the RH group.

Information abstracted from registered operative records included patients age, diagnosis using the International Federation of Gynecology and Obstetrics (FIGO) stage classification, procedure performed, estimated blood loss (EBL) at surgery, operative time, use of amputation of uterine corpus following cesarean delivery, intraoperative transfusion, intraoperative complications, histology, period of follow-up since surgery, and presence or absence of recurrence. For the neonatal information, gestational age at delivery, infant weight, and Apgar scores were collected.

Operative time was defined as the interval between the time at which the surgical procedure was started and the time at which it was completed, as counted by a digital timer. EBL was calculated by adding the amount of suctioned blood to measured blood by automated scale based on surgical gauze weight. A surgical complication was defined as intraoperative damage to the bowel, bladder, ureter, a large vessel, an EBL of 2000 ml or more (major blood loss), or significant medical complications. The indication for and decision to perform a transfusion were determined by the anesthesiologist during the surgery.

Amputation of uterine corpus during CRH was defined as the removal of the uterine corpus at the same anatomical incision level as low transverse uterine incision for cesarean delivery following ligation of the uterine arteries. The surgical technique is based on that of subtotal abdominal hysterectomy [9]. The low transverse uterine incision was made anatomically far from the cervical cancer lesion. Following the amputation of the uterine corpus, the amputated site was immediately closed with a running locked suture and radical hysterectomy was performed.

Nonparametric statistical analysis was performed with the Wilcoxon signed-rank test or a Mann–Whitney U test. Two-tailed tests with $p < 0.05$ were considered significant. Subjects for whom there were missing data for any variable were excluded from the analysis. The analysis utilized Statistical Package for Social Scientists software (SPSS, Inc., version 12.0, Chicago, IL, USA).

The study protocol was approved by the local ethical committee for the Osaka Rosai Hospital and the Osaka University Graduate School of Medicine, Osaka, Japan.

Results

In total, five cases of CRH were performed for pregnancy complicated by cervical cancer during the six-year study period. In three (60%) of these cases, the planned amputation of uterine corpus was performed immediately following cesarean delivery. Two (40%) of these cases were CRH without amputation of uterine corpus. There were 209 cases of RH for nonpregnant women. Five of the 214 cervical cancer cases that underwent surgical treatment were complicated by pregnancy (2.3%).

Table 1 shows the patient characteristics for the CRH group and the RH group. Mean patient age for the CRH group was younger than it was for the nonpregnant RH group: 32.0 years of age (range 24–37) versus 48.4 years of age (range 18–75), $p < 0.001$. The intraoperative performances for the two groups were also compared. The difference in mean operative time between the groups was not statistically significant: 276.6 min for the CRH group (range 160–425) versus 297.3 min for the RH group (range 147–645), $p = 0.66$. However, the mean EBL was significantly larger in the CRH group: 2106.6 ml (range 730–4150) versus 858.8 ml for the RH group (range 150–4770), $p < 0.001$. Cervical cancer complicating pregnancy had an earlier FIGO stage than nonpregnant cervical cancer: 0% for the CRH group versus 16.3% for the RH group at stage IIB, $p < 0.001$. The differences in the proportions of squamous cell carcinoma and adenocarcinoma between groups were not statistically significant.

The difference in the prevalence of intraoperative transfusion between groups was not statistically significant (40 vs. 50.7%, $p = 0.68$). There was a higher rate of major surgical complications in CRH subjects (40 vs. 11.0%, $p = 0.047$). These complications included two (40%) cases

of major blood loss in the CRH group, as well as two (1.0%) cases of bladder injury, two cases (1.0%) of ureter injury, and 19 (9.1%) cases of major blood loss in the nonpregnant RH group.

Table 2 shows the patient characteristics of the five CRH cases. Demographics were divided up based on the use of amputation of uterine corpus following cesarean delivery. All cervical cancer cases were diagnosed during the pregnancy using a screening cytology evaluation. Mean gestational age for cesarean delivery was 31.9 weeks (range 29.9–33.9). All of the neonates were appropriate for gestational age, and betamethasone was given for fetal lung maturity. A low transverse cesarean section was performed for all cesarean deliveries. No intraoperative tumor exposures to the surgical field were observed in the three cases of CRH where planned amputations of uterine corpus were performed. None of the five CRH cases underwent paraaortic lymphadenectomy.

The follow-up periods ranged from 8 to 76 months, and one subject showed a recurrence involving metastasis to Virchow's lymph nodes. This subject underwent amputation of the uterine corpus during CRH.

As shown in Table 2, amputation of the uterine corpus following cesarean section seems to affect the intraoperative performance of CRH. Thus, further statistical evaluation was performed for the CRH subjects based on the use of amputation of the uterine corpus (Table 3). Use of amputation of the uterine corpus during CRH contributed to significant reductions in operative time and EBL: operative time, 186.0 min (range 160–228) versus 412.5 min (range 400–425), $p = 0.043$; EBL, 1034.3 ml (range 730–1540) versus 3715.0 ml (range 3280–4150), $p = 0.043$. None of the patients who underwent amputation of the uterine corpus required an intraoperative transfusion: 0 versus 100%, $p = 0.046$. Mean EBL in the CRH group with amputation of the uterine corpus was similar to that in the RH group [1034.3 ml (range 730–1540) versus 858.8 ml (range 150–4770), $p = 0.17$], while the mean EBL in the CRH group without amputation of the uterine corpus was significantly larger than that in the RH group [3715.0 ml (range 3280–4150) versus 858.8 ml (range 150–4770), $p = 0.017$].

Table 1 Patient characteristics

Subjects	CRH $n = 5$	RH $n = 209$	p value
Age	32.0 (24–37)	48.4 (18–75)	<0.001
Stage IA	1 (20.0%)	13 (6.2%)	0.23
Stage IB	3 (60.0%)	129 (61.7%)	0.88
Stage IIA	1 (20.0%)	22 (10.5%)	0.52
Stage IIB	0	34 (16.3%)	<0.001
SCC	3 (60%)	97 (46.4%)	0.67
Adenocarcinoma	2 (40%)	60 (28.7%)	0.61
Op. time (min)	276.6 (160–425)	297.3 (147–645)	0.66
EBL (ml)	2106.6 (730–4150)	858.8 (150–4770)	<0.001
Transfusion	2 (40.0%)	106 (50.7%)	0.68
Surgical complication	2 (40.0%)	23 (11.0%)	0.047

Mean with range or mean with percentage is shown. The nonparametric Wilcoxon signed-rank test or Mann–Whitney *U* test was used for the statistical analysis. Stage description is based on the FIGO classification

CRH cesarean radical hysterectomy, *RH* radical hysterectomy, *EBL* estimated blood loss, *Op. time* operative time, *SCC* squamous cell carcinoma

Discussion

Cervical cancer during pregnancy is the most common gynecologic malignancy that complicates pregnancy [1]. Annually, 3% of 14,000 newly diagnosed cervical cancer cases are diagnosed during pregnancy in the United States

Table 2 Patient characteristics for cesarean radical hysterectomy

Age	Stage	GA at delivery	Infant weight	Apgar scores	Op. time	EBL	Transfusion	Histology	Follow-up	Status
Planned amputation of uterine corpus										
37	IB1	32 + 6/7	1882	8/9	170	730	None	Mucinous adenocarcinoma	36	Rec*
24	IA2	30 + 3/7	1418	8/9	228	833	None	Papillary squamous cell carcinoma	48	NED
30	IIA	33 + 6/7	2432	8/9	160	1540	None	Squamous cell carcinoma	8	NED
No amputation of uterine corpus										
32	IB1	29 + 6/7	1644	7/8	400	3280	PRBC4	Endometrioid adenocarcinoma	48	NED
37	IB1	32 + 3/7	1760	8/9	425	4150	PRBC14, FFP12	Squamous cell carcinoma	76	NED

Stage description is based on the FIGO classification. Apgar scores are 1 and 5 min, respectively

GA at delivery gestational age at delivery (weeks), *Op. time* operative time (min), *EBL* estimated blood loss (ml), *PRBC* packed red blood cells (units), *FFP* fresh frozen plasma (units), *Follow-up* period of patient follow-up (months), *NED* no evidence of disease, *Rec** recurrence at Virchow's lymph nodes at 35 months