

Radical hysterectomy for stage IIB cervical cancer: a review

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Patients with stage IIB cervical cancer in some countries in Europe and Asia especially in Japan are usually treated with radical hysterectomy and pelvic lymphadenectomy. Extrauterine diseases, ie, nodal metastases, parametrial invasion, and intraperitoneal spread, can be readily identified. We present the literature review of radical hysterectomy in stage IIB cervical cancer by searching data since 1980 from Medline, and we found that the parametrial involvement of patients in this stage was only 21–55%, the incidence of pelvic node metastases was about 35–45%, and 5-year survival rate was between 55% and 77%. Lymph node metastases and the number of positive nodes were significant prognostic factors of patients in this stage.

KEYWORDS: cervical cancer, radical hysterectomy, stage IIB.

According to the National Comprehensive Cancer Network guideline version 1, 2004, the treatment of choice for stage IIB cervical cancer is concurrent cisplatin-based chemoradiation therapy. However, in some countries in Europe and Asia especially in Japan, these patients are generally treated with radical hysterectomy and pelvic lymphadenectomy using the Okabayashi or Tokyo technique. In 1983, the Japan Society of Obstetrics and Gynecology reported that 62.7% of stage IIB cervical cancer patients were treated with radical hysterectomy⁽¹⁾. The advantages of this approach are avoiding the long-term complications of radiation therapy and the morbidity of concurrent chemoradiation in patients who did not have high-risk pathologic factors, ie, positive nodes, parametrial

invasion, and involved surgical margins. In young patients, ovarian function and vaginal pliability can also be preserved. On the other hand, in case of lymph node metastases, the ovaries may be transposed outside the radiation field. Occult extrauterine diseases such as nodal involvement, parametrial invasion, or intraperitoneal spread can be identified, and removal of bulky positive nodes may improve survival after adjuvant radiation. Additionally, removal of the primary tumor may preclude some radioresistant cervical cancers. The disadvantage of primary surgery for stage IIB cervical cancer is the risk of morbidity associated with receiving combined treatment of chemoradiation following the radical operation.

This article presents the review of primary surgical treatment for stage IIB cervical cancer. We conducted a literature search on Medline using PubMed, from January 1980 to April 2004, using search terms “cervical cancer,” “stage IIB,” “surgical treatment,” and “hysterectomy.” Only English articles were included. All

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identified articles that reported on the same aspects of prognostic factors, outcomes, and complications of radical surgery for stage IIB cervical cancer were included in the review. This review will summarize the incidence of parametrial invasion and pelvic node metastases in stage IIB cervical cancer, the relationship between parametrial invasion and pelvic node metastases, the adjuvant treatment after surgery, the prognostic factors, the outcomes, and also the complications of this treatment approach.

The parametrial invasion

Among the seven studies reporting performing radical hysterectomy in patients with stage IIB cervical cancer, shown in Table 1, parametrial involvement was pathologically confirmed in approximately 21–55%^(2–8). These findings imply that approximately one half to three fourths of patients with clinical stage IIB cervical cancer are overstaged. The discrepancy between the clinical and the pathologic stages is most likely caused by difficulty in discriminating parametrial extension from inflammatory change, endometriosis, adhesion, and irregular shape of large cervical tumor^(4,7). Most authors^(2,5,6,8) except Kamura *et al.*⁽⁷⁾ did not mention whether the clinical staging procedure for parametrial evaluation was carried out under anesthesia or not. Kamura *et al.*⁽⁷⁾ studied the histopathologic prognostic factors in stage IIB cervical cancer patients treated at Kyushu University Hospital, Japan. There were 133 stage IIB patients. The clinical staging procedures consisted of the pelvic examination under anesthesia, cystoscopy, colposcopy, proctoscopy, chest X-ray, and intravenous pyelogram. Of these patients, radical surgery was not performed in 26 patients. Among the remaining 107 patients, radical hysterectomy was abandoned in 25

patients because of the following reasons: suspicious para-aortic node metastasis (5), fixation of pelvic lymph nodes with iliac vessels (7), and unable to separate the cervix and vagina from the bladder (14). Consequently, there were 82 patients undergoing radical hysterectomy. Parametrial invasion was identified as high as 45% from this series.

Matsuyama *et al.*⁽²⁾, from the same institute as Kamura, divided the parametrial invasion into two groups according to the site of involvement, ie, the inner half and the outer half; the 5-year survival rate of these two groups were not significantly different, at 62.8% and 65.7%, respectively.

Burghardt *et al.*⁽⁵⁾, from the University Hospital of Graz, Austria, classified the parametrial involvement into four patterns, ie, the continuous, the discontinuous, the involvement of parametrial nodes, and the involvement of parametrial vessels. The most common pattern was the involvement of parametrial nodes (21.6%), followed by the continuous pattern (8.7%), the involvement of parametrial vessels (6.7%), and the discontinuous pattern (3.6%). Evaluation of the parametrium shows that there are many lymph nodes and lymphatic vessels in both the inner and the outer part of the parametrium; these areas can be the potential sites of tumor spreading. The tumor mainly spreads to the adjacent parametrium by tumor cell emboli and lymph node involvement⁽⁶⁾. Girardi *et al.*⁽⁶⁾ from the same institute as Burghardt demonstrated that parametrial involvement was related to pelvic node metastasis. Approximately 80% of patients with parametrial node metastasis had positive pelvic nodes, while 74% of those with negative parametrial nodes would have had negative pelvic nodes.

From these studies, it can be concluded that the incidence of parametrial invasion in stage IIB cervical cancer is at most 55%. This means that nearly one half of the patients are overstaged.

Table 1. Parametrial invasion and node metastases in stage IIB cervical cancer patients treated with radical hysterectomy

Authors	Study period	Year	Number of patients	Parametrial invasion (%)	Pelvic node metastases (%)	Para-aortic node metastases (%)
Matsuyama <i>et al.</i> ⁽²⁾	1973–1977	1984	99	42	—	—
Inoue and Okumura ⁽³⁾	1965–1977	1984	223	34	38.6	—
Inoue and Morita ⁽⁴⁾	1965–1986	1990	295	51.2	43	—
Noguchi <i>et al.</i> ⁽⁹⁾	1950–1984	1987	239	—	33.9	—
Burghardt <i>et al.</i> ⁽⁵⁾	1971–1985	1987	195	29.7	44.1	—
Girardi <i>et al.</i> ⁽⁶⁾	1971–1986	1989	219	21.5	40.6	—
Kamura <i>et al.</i> ⁽⁷⁾	1979–1988	1993	82	45	35	—
Okada <i>et al.</i> ⁽¹⁰⁾	1988–1994	1998	30	—	36.7	—
Sakuragi <i>et al.</i> ⁽¹¹⁾	1982–1995	1999	97	—	39.2	7.2
Kawagoe <i>et al.</i> ⁽⁸⁾	1984–1996	1999	24	55	45.8	—
Takeda <i>et al.</i> ⁽¹²⁾	1982–1995	2002	88	—	36.4	4.5

The pelvic node metastases

There were ten articles reporting the incidence of pelvic node metastases in stage IIB cervical cancer patients undergoing radical hysterectomy as shown in Table 1. The incidence of pelvic node metastases was approximately 35–45.8%^(3–12). Para-aortic node metastases were found in 4.5–7.2% of patients in this stage^(11,12). The most common sites of pelvic node metastases were the hypogastric⁽⁹⁾ and the obturator⁽¹²⁾. The incidence of node metastases increased with the size of cervical tumor⁽⁵⁾.

In 1984, Inoue and Okumura⁽³⁾ from the Aichi Cancer Center in Nagoya, Japan, noted that most of the stage IIB cervical cancer patients had only one positive node (38%), while two, three, and more than four positive nodes were detected in 22%, 8%, and 20%, respectively. Of note is that 12% had unresectable positive nodes. Six years later, these authors reported their experience with extension of the study period from 1965–1977 to 1965–1986, with the number of patients increased from 223 to 295⁽⁴⁾. In this later report, they revealed that the incidence of positive pelvic nodes increased from 38% to 43%.

There were two couples of studies from the same institutes, one from the University of Graz, Austria, reported 41–44% incidence of pelvic node metastases in stage IIB cervical cancer^(5,6). The other one from the Hokkaido University of Medicine, Japan, showed such incidence of 37–39%^(11,12).

In 2002, Winter *et al.*⁽¹³⁾ from the University of Graz, Austria, evaluated the parametrial spread in patients who had negative pelvic nodes. They performed radical hysterectomy in 556 patients with stage IB, IIA, and IIB cervical cancer. Among 351 patients with negative nodes, 35 were in stage IIB. Of

these 35 patients, parametrial involvement was identified only in 17%.

Benedetti-Panici *et al.*⁽¹⁴⁾ evaluated the relation between parametrial and pelvic node involvement in patients with stage IB–IIA cervical cancer undergoing radical hysterectomy. The hysterectomy specimens were processed with the giant section technique to obtain a thorough three-dimensional pathologic assessment of the parametrium. Clinically, undetected parametrial involvement was found by pathologic examination in 31%, 63%, and 58% of stage IB1, IB2, and IIA patients, respectively. Metastases to the pelvic nodes were always associated with parametrial invasion.

In conclusion, the incidence of pelvic node metastases in stage IIB cervical cancer is approximately 35–45%. Pelvic node metastases are always associated with parametrial involvement.

The relationship between parametrial involvement and pelvic node metastases

Seven studies reported the relationship between the parametrial involvement and the positive pelvic nodes in stage IB–IIIB cervical cancer patients treated with radical surgery^(2–7,9) as shown in Table 2. Of these, only one study from Kyushu University, Japan, demonstrated the relationship of parametrial status and the incidence of positive pelvic nodes in patients with stage IIB cervical cancer. Pelvic node metastases increased three times from 13.3% to 37.8% when the parametrium was involved with the tumor⁽⁷⁾. Invasion of the tumor to the parametrium significantly correlated with the spreading of tumor to the pelvic nodes. Such incidence increased two to six times in patients with positive parametrium.

Table 2. The relationship between parametrial status and pelvic node metastases

Authors	Year	Stage	Parametrium	Pelvic node metastases (%)
Noguchi <i>et al.</i> ⁽⁹⁾	1987	IB–IIIB	Positive	54.8
			Negative	8.5
Burghardt <i>et al.</i> ⁽⁵⁾	1987	IB–IIIB	Positive	75.3
			Negative	23.4
Inoue and Okumura ⁽³⁾	1984	IB, IIA, IIB	Positive	57.9
			Negative	28.6
Inoue and Morita ⁽⁴⁾	1990	IB, IIA, IIB	Positive	29.2
			Negative	14.2
Matsuyama <i>et al.</i> ⁽²⁾	1984	IB, IIA, IIB	Positive	42
Giardi <i>et al.</i> ⁽⁶⁾	1989	IB–IIB	Positive	81
			Negative	26
Kamura <i>et al.</i> ⁽⁷⁾	1993	IIB	Positive	37.8
			Negative	13.3

Matsuyama *et al.*⁽²⁾ reported the 42% incidence of pelvic node metastases when the parametrium was involved in patients with stage IB–IIIB cervical cancer who were treated with radical hysterectomy. However, such incidence in cases of negative parametrium was not mentioned. Interestingly, two series, one from Austria, another from Japan, reported the use of surgical treatment for stage IIIB cervical cancer^(5,9). From these studies, it can be concluded that parametrial involvement is strongly associated with pelvic node metastases.

Adjuvant treatment after surgery

After radical operation for stage IIB cervical cancer patients, adjuvant radiations are usually administered if any high-risk pathologic factors, ie, positive pelvic nodes, parametrial invasion, and involved surgical margins, are identified^(2–5). Some authors also gave adjuvant radiation to patients who had deep cervical stromal invasion^(2,7,10) or prominent lymphovascular space invasion (LVSI)^(2,12). With various criteria for postoperative radiation therapy, the percentage of stage IIB cervical cancer patients who received adjuvant treatment in one study was surprisingly high at 72%⁽⁷⁾. Recently, the Japanese Patterns of Care Study Working Group⁽¹⁵⁾ has conducted an extramural survey of 73 institutions in Japan on the postoperative radiation between September 1998 and March 2001. The study revealed that only 33% of stage IIB cervical cancer patients received adjuvant radiation. The summary of the indications for adjuvant radiation after surgery for stage IIB cervical cancer is shown in Table 3.

Currently, concurrent cisplatin-based chemoradiation is recommended in patients who need adjuvant radiation after radical surgery for early-stage cervical cancer^(16,17). However, Kawagoe *et al.*⁽⁸⁾ gave chemo-

therapy alone to patients who had positive surgical margins or lymph node involvement.

Various types of adjuvant treatment have been used for cervical cancer patients who have high-risk pathologic factors after the operation. The Austrian Gynecologic Oncology Group has conducted a prospective, randomized, multicenter study to compare the values of adjuvant radiation, adjuvant chemotherapy, and expectant treatment in IB, IIA, and IIB cervical cancer patients who had high-risk factors identified after radical hysterectomy. Adjuvant chemotherapy or radiation did not improve the survival or reduce the recurrence after the operation when compared with observation alone⁽¹⁸⁾.

In conclusion, most authors advised radiation in patients who had high-risk pathologic factors after the operation. The benefit of adjuvant treatment in these patients is inconclusive and needs further study in a prospective randomized fashion.

The prognostic factors

There were nine studies using multivariate analysis to determine the significance of various prognostic factors after radical hysterectomy for cervical cancer as shown in Table 4. Kamura *et al.*⁽⁷⁾ studied only stage IIB cervical cancer, while other authors also included stage IB, IIA, or even IIIB. Lymph node metastases and the number of positive nodes were significant prognostic factors in all studies^(2,4,5,7,8,10–12,19), while parametrial involvement affected the patient survival in only four studies^(2,4,10,12). The clinical stage of cervical cancer influenced treatment outcomes in two studies^(8,19). Kawagoe *et al.*⁽⁸⁾ noted that the tumor size was also an important prognostic factor, while LVSI and deep stromal invasion were found to affect patient survival in the series of Sakuragi *et al.*⁽¹¹⁾.

Takeda *et al.*⁽¹²⁾ had pathologically stratified the cervical cancer patients after treatment with radical operation into three groups, ie, low-risk group, intermediate-risk group, and high-risk group. The low-risk group consisted of patients with tumor confined to the uterus and without LVSI. The intermediate-risk group included patients with tumor confined to the uterus with associated parametrial invasion or pelvic node metastasis. The high-risk group comprised patients with pure adenocarcinoma with associated parametrial involvement or pelvic node metastases and patients with common iliac or para-aortic node metastases. The estimated 5-year survival rates of these three groups were 100%, 85.5%, and 25%, respectively.

Aoki *et al.*⁽²⁰⁾ studied the prognostic factors in 59 cervical cancer patients with positive nodes after

Table 3. Indications for adjuvant radiotherapy

Authors	PMI	Positive LN	Positive margins	Others
Okada <i>et al.</i> ⁽¹⁰⁾	+	+	+	DSI
Kawagoe <i>et al.</i> ^{(8)a}	–	+	+	—
Takeda <i>et al.</i> ⁽¹²⁾	+	+	–	LVSI, ovarian metastasis
Inoue and Morita ⁽⁴⁾	+	+	–	—
Matsuyama <i>et al.</i> ⁽²⁾	+	+	+	LVSI, DSI
Kamura <i>et al.</i> ⁽⁷⁾	+	+	–	DSI
Trattner <i>et al.</i> ⁽¹⁹⁾	+	+	+	LVSI

PMI, parametrial involvement; LN, lymph node; DSI, deep stromal invasion; LVSI, lymph vascular space invasion; +, adjuvant radiation; –, no adjuvant radiation.

^aAdjuvant chemotherapy.

Table 4. The significant prognostic factors

Authors	Year	Stage	Total number of patients	Number of stage IIB patients	The prognostic factor
Okada <i>et al.</i> ⁽¹⁰⁾	1998	IB–IIB	104	30	+ PM, + LN
Burghardt <i>et al.</i> ⁽⁵⁾	1987	IB–IIIB	800	195	Number of positive nodes
Inoue and Morita ⁽⁴⁾	1990	IB, IIA, IIB	875	295	Number of positive nodes, + PM
Kawagoe <i>et al.</i> ⁽⁸⁾	1999	IB, IIA, IIB	128	24	Stage, tumor size, + LN
Matsuyama <i>et al.</i> ⁽²⁾	1984	IB, IIA, IIB	255	99	Number of positive nodes, + PM
Takeda <i>et al.</i> ⁽¹²⁾	2002	IB, IIA, IIB	187	88	+ LN, + PM, LVSI, adenocarcinoma
Kamura <i>et al.</i> ⁽⁷⁾	1993	IIB	107	107	Number of positive nodes
Trattner <i>et al.</i> ⁽¹⁹⁾	2001	IB, IIA, IIB	115	35	Stage, + LN
Sakuragi <i>et al.</i> ⁽¹¹⁾	1999	IB, IIA, IIB	208	97	LVSI, DSI, + LN (para-aortic nodes, bilateral pelvic nodes, common iliac nodes)

PM, parametrium; LN, lymph node; LVSI, lymph vascular space invasion; DSI, deep stromal invasion; +, positive.

radical hysterectomy followed by adjuvant pelvic radiation. Of these patients, 37 were in stage IIB cervical cancer. The authors noted that both the number of positive nodes (≥ 2) and the parametrial involvement were significantly associated with decreased disease-specific survival. The 5-year recurrence rate in patients with both prognostic factors was as high as 70%, while no recurrence was found in patients who had one positive node and no parametrial invasion.

Among the patients with stage IIB cervical cancer who had negative nodes, tumor size and LVSI were the significant prognostic factors by multivariate analysis in the study of Comerci *et al.*⁽²¹⁾. Winter *et al.*⁽¹³⁾ showed that parametrial involvement was of no prognostic significance in 149 stage IIB cervical cancer patients who had negative nodes.

It can be concluded that the number of positive nodes is a strongly significant prognostic factor, while the influence of parametrial invasion on patient survival is still controversial in patients with stage IIB cervical cancer.

The outcomes

There were four studies that reported the overall survival of stage IIB cervical cancer patients treated with radical hysterectomy as shown in Table 5. Matsuyama *et al.*⁽²⁾ found that among 99 patients with stage IIB

cervical cancer, 29 died or had disease recurrence. Three patients died of radiation complications, and one died of intercurrent disease. The overall 5-year survival rate was approximately 71%. Burghardt *et al.*⁽⁵⁾ reported a 5-year survival rate of 77% in 191 patients with stage IIB cervical cancer treated with radical surgery, higher than that of 63% in the series of Trattner *et al.*⁽¹⁹⁾. The outcome of stage IIB patients was worse in the study of Aoki *et al.*⁽²⁰⁾, which revealed a 5-year survival rate of 55% in 37 stage IIB cervical patients who had positive nodes.

The nodal status and the number of positive nodes play an important role on the survival outcome of patients with cervical cancer. In the series of Noguchi *et al.*⁽⁹⁾, the survival of patients decreased with the increasing number of positive nodes. The 5-year survival rates of patients who had negative nodes was 83%, while those of the patients who had 1, 2–3, and ≥ 4 positive nodes were 64.4%, 43.1%, and 30%, respectively. Girardi *et al.*⁽⁶⁾ studied 219 patients with stage IIB cervical cancer treated with radical hysterectomy. The 5-year survival rate in cases of negative parametrial nodes was high at 81% and dropped to 54% when the parametrial nodes were positive. In the report of Inoue and Morita⁽⁴⁾, which included 223 patients with stage IIB cervical cancer, the 5-year survival rate of patients with positive nodes (57%) was significantly lower than that of patients with negative nodes (91%). The 5-year survival rate decreased to 38.5% when the number of positive nodes was ≥ 4 . In the study of Okada *et al.*⁽¹⁰⁾, the outcome of patients with parametrial extension was not different from those with positive nodes. The 5-year survival rates of both groups were 76.6% and 76.3%, respectively, while that of patients with only deep stromal invasion was still high at 89.3%.

In conclusion, the 5-year survival rate of stage IIB cervical cancer patients treated with radical

Table 5. The 5-year survival rate

Authors	Year	5-year survival rate (%)
Aoki <i>et al.</i> ⁽²⁰⁾	2000	55.2
Trattner <i>et al.</i> ⁽¹⁹⁾	2001	62.9
Matsuyama <i>et al.</i> ⁽²⁾	1984	70.7
Burghardt <i>et al.</i> ⁽⁵⁾	1987	76.9

hysterectomy ranged between 55% and 77%. The most important prognostic factor is the number of positive nodes.

The complications

There were few studies reporting the complications of surgical treatment in patients with stage IIB cervical cancer. The complications increased when the patients received adjuvant radiation after radical hysterectomy compared with surgery alone^(2,22). The complications also increased with radiation dosage. Bowel obstruction, fistula, and rectal hemorrhage occurred in 8.5% and 13.6% of patients receiving radiation of 5000 cGy and 6000 cGy, respectively⁽²⁾.

Conclusion

Patients with stage IIB cervical cancer may be treated with radical hysterectomy and pelvic lymphadenectomy. Approximately 50–80% of patients are overstaged due to difficulty in differentiation between the parametrial involvement and the inflammatory change of the paracervical tissue. Parametrial invasion significantly correlated with pelvic node metastases. Adjuvant radiation is recommended in patients who have high-risk pathologic factors, ie, positive nodes, parametrial involvement, and involved surgical margins. The strongest prognostic factor is the number of positive nodes. The complications appear to be higher in patients who receive both surgery and adjuvant radiation.

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