CHAPTER II

LITERATURE REVIEW

2.1 Clinical and pathological prognostic factors in cervical cancer patients treated by radical hysterectomy

Various studies tried to investigate the prognostic factors in surgical treated cervical cancer. Some authors evaluated only node positive or node negative patients, although the majority of these included both. Table 2.1 included the literatures, that studied the prognostic factors in cervical cancer patients primarily treated by radical surgery using multivariable analysis.[6,7,11-13,53-70] The end points for comparison were overall survival (OS) or disease free survival (DFS) or disease specific survival (DSS) or recurrent rate (RC). All these studies include both node positive and node negative patients. Most patients were in stage Ib although some studies contained patients with stage Ia, IIa, and IIb. The use of postoperative therapy (mainly radiation) varied according to the author's recommendation and might not be uniform even in the given institution. All cell types were included, although some reports were restricted to a given cell type. In most incidences, neuroendocrine histotypes were excluded.

Factors that significantly associated with survival or recurrent rate in multivariable analysis included lymph node metastasis (LNM),[6-8,11-13,54,57,59-64,68-70] tumor size,[12,55,57,58,64-67,69] cervical stromal involvement or depth of invasion (DI),[53,55,56,58,61,63,64,66-68] lymph-vascular space invasion (LVSI),[11,13,54,55,58] histological cell type,[6,7,11,12,67,70] tumor differentiation or tumor grade,[61] parametrial invasion (PI),[11,64] surgical margin involvement,[63] stage,[7] and age at diagnosis.[6]

There are only few literatures evaluated the prognostic factors in patients with node negative cervical cancer patients treated by radical hysterectomy.

Table 2.1 Clinical and pathological independent risk factors in surgical treated cervical cancer.

Authors	Year	No of patients	End outcome	Significant prognostic factors in multivariable analysis
Gauthier[53]	1985	100	OS	DI
Kenter[54]	1988	213	OS	LNM, LVSI
Delgado[55]	1990	645	DFS	size, LVSI, DI
Hopkins[56]	1991	213	OS	DI
Kamura[12]	1992	345	OS	size, histo, LNM
Finan[57]	1996	229	OS	size, LNM
Look[58]	1996	813	DFS	size, LVSI, DI
Garipagaoglu[59]	1998	100	OS,DFS	LNM
Obermair[60]	1998	163	RC	LNM
Yuan[61]	1998	443	OS	grade, LNM, DI
Frigerio[62]	1998	103	OS	LNM
Snijders-Keiholz[63]	1999	233	DFS	LNM, DI, surgical margin
Hellebrekers[64]	1999	294	DFS	size, LNM, DI, PI
Kristensen[65]	1999	125	OS	size
Lai[66]	1999	872	OS,DFS	size, DI
Tsai[67]	1999	222	DSS	size, PI
Yuan[68]	1999	1115	RC,OS	LNM, DI
Kim[6]	2000	366	OS	age, histo, LNM
Nakanishi[69]	2000	566	DFS	size, hitso, LNM
Atasu[13]	2000	200	DFS,OS	LNM, LVSI
Manusirivithaya[7]	2001	685	RC	Stage, histo, LNM
Trattner[70]	2001	112	OS	histo, LNM
Graflund[8]	2002	172	DFS	LNM
Takeda[11]	2002	187	OS	histo, LNM, LVSI, PI

OS=overall survival, DFS=disease free survival, RC=recurrent rate, DSS=disease specific survival
DI=depth of invasion, LNM=lymph node metastasis, LVSI =lymph-vascular space invasion
histo = histological type (squamous vs non-squamous, or squamous vs. adenocarcinoma)
PI = parametrial invasion

In 1991, Smiley et al[71] evaluated 95 patients with squamous cell cervical carcinoma less than 5 cm. in diameter, tumor invasion greater than 5 mm., negative lymph nodes, and clear surgical margins, who underwent radical hysterectomy with bilateral pelvic lymphadenectomy, to see whether other clinical or histopathological factors were predictive of tumor recurrence. The 5-year acturial survival rate was 89% with the median follow up of 65 months. Nine patients (9.5%) developed recurrent disease. Degree of differentiation was the only histopathologic factor that associated with recurrence (p=0.02). Increasing depth of invasion associated closely with increasing width, but was not associated with increased incidence of recurrence. Tumors with lymph-vascular space invasion were more likely to have an infiltrating tumor-stromal border but not an increased recurrence risk.

In 1997, Schorge et al[17] retrospectively reviewed the records of 171 patients with lymph node negative stage Ib and IIA cervical cancer primarily treated with radical hysterectomy and pelvic lymphadenectomy. Among these, 32% received adjuvant radiotherapy. The decision to recommend radiotherapy was individualized, based on the surgical-pathological findings. The median duration of follow-up was 84 months (range 27-249 months). Twenty-eight patients (16%) developed recurrent diseases. Factors predictive of recurrence included LVSI (p=0.003) and grade 3 histology (p=0.04).

In 1997, Samlal et al[18] retrospectively reviewed the records of 196 patients with lymph node negative stage Ib cervical cancer primarily treated with radical hysterectomy and pelvic lymphadenectomy. Twenty-six patients (13.3%) received adjuvant radiotherapy. The median duration of follow up for censored patients was 68 months. The estimated 5-year DFS was 92%. Fifteen patients experienced recurrent diseases (7.7%). In multivariate Cox regression analysis for DFS, adenocarcinoma (p=0.003), fraction of cervical stroma penetration (p=0.01) and extensive stromal inflammatory cell infiltrate (p=0.04) were the only independent factors that were

predictive of recurrence. In the Cox model, the hazard increased by an estimated factor of 4.6 (95%CI: 3.6-5.9) per one-third increase in the fraction of cervical stroma penetration. Patients with adenocarcinoma had an estimated 2.3 (95%CI: 1.3-4.0) times higher hazard than patients with squamous cell carcinoma. For the stromal inflammatory cell infiltrate factor, the hazard ratio was 2.5 (95% CI: 1.0-6.2) when there was an extensive response compared with a light or moderate response. Based on hazard ratios, the following risk factors were defined: adenocarcinoma, extensive infiltrate stroma response, and cervical stromal penetration $\geq$ 2/3. The 5-year DFS for patients without any risk factor was 97% , where as for patients with one and more than one risk factor were 98% and 81% respectively.

In the year 2002, Koidara et al[16] performed retrospective analysis to evaluate the outcome of postoperative radiotherapy for 68 stage Ib-IIb cervical cancer patients without lymph node metastasis. All patients underwent radical (n=63) or modified radical (n=5) hysterectomy. Criteria for postoperative radiotherapy among these patients were as follows : deep stromal invasion ($\geq$1/2; n=63), positive parametrial invasion (n=38), positive or close (<5mm.) surgical margin (n=21). The risk score was assessed by large tumor size ($\geq$40 mm.), presence of LVSI and deep stromal invasion ($\geq$1/2). The patients were divided into groups with 0-1 risk or 2-3 risk as a function of these criteria. At the end of the study, 8 patients died of disease while 2 died of intercurrent disease. The median follow up time for 58 survivors was 114 months (46-208 months). Patients with 0-1 risk factor had a 5-year DFS of 93.9% compared to 77.1% in those with 2-3 risk factors (p=0.018). In multivariate model, only risk score (p=0.027) and overall treatment time (p=0.043) were proved to be significant prognostic factors.

In the year 1999; Sedlis et al[72] reported the result from the Gynecologic Oncology Group (GOG) study of a randomized trial of pelvic radiation therapy (RT)

versus no further therapy (NFT) in selected patients with node negative stage IB carcinoma of the cervix after radical hysterectomy and pelvic lymphadenectomy. Two hundred seventy-seven women with one of the combination risk factors as defined in Table 2.2 were eligible to enter this study, 137 were randomized to RT and 140 to NFT [Twenty-one (15%) in the RT group and 39 (28%) in the NFT group had a cancer recurrence. Life table analysis indicated a statistically significant (47%) reduction in risk of recurrence (relative risk = 0.53, p = 0.008, one-tail) among the RT group, with recurrence-free rates at 2 years of 88% versus 79% for the RT and NFT groups, respectively. The authors concluded that adjuvant pelvic radiotherapy following radical surgery reduces the number of recurrences in women with Stage IB cervical cancer.

Since patients treated with the combination of surgery and radiation may be more likely to develop serious complications.[5,73] Identification of those patients most likely to benefit from postoperative adjuvant treatment is essential. Based on the clinical and pathological prognostic factor, combination of factors may be required to define this high-risk group. However, there is no consensus on the criteria to select this high-risk group. The study of Sedlis et al[72] is the only randomized study, which evaluated the benefit of adjuvant radiotherapy in high-risk node negative cervical cancer patients.

Though recurrence was significantly decreased in patients receiving adjuvant treatment, this study also demonstrated that 78% of this high-risk group (based on criteria in Table 2.2) did not have tumor recurrence even without adjuvant treatment. These 78% were the patients who did not gain benefit from adjuvant therapy, but certainly had higher risk of serious complications. Hence, many studies still try to find other prognostic factors for cervical cancer including biomolecular factors.

Table 2.2 Eligibility Criteria in the study of Sedlis et al. [71]

Capillary lymphatic space	Stromal invasion	Tumor size
Positive	Deep 1/3	Any
Positive	Middle 1/3	$\geq$ 2 cm
Positive	Superficial 1/3	$\geq$ 5 cm
Negative	Deep or middle 1/3	$\geq$ 4 cm

2.2 Prognostic significance of bcl-2 in cervical cancer

There are many studies examined the prognostic significance of bcl-2 in cervical cancer (Table 2.3). Almost all of these studies are descriptive studies, which retrospectively reviewed a set of cervical cancer patients. They performed the immunohistochemical staining using anti bcl-2 antibody and compared the result of the staining with the overall survival and/or relapse free survival. Some studies demonstrated that patients with bcl-2 positive tumor had longer survival. [25,40-44] Some reported that bcl-2 positive tumor had shorter survival,[45-46] while some can not demonstrate the significance of bcl-2.[47-52] However, there seem to be biases in some of these studies, for example :

1. not clarify how they recruited the patients into the study, usually, they only stated that these patients had been diagnosed or treated during some period but not stated whether they studied consecutive patients.[25,43-45,47]
2. not clarify whether they had blinded the interpretators about the clinical outcome of the patients.[25,42,45,47,52]
3. the limited number of the study patients.[40,45,48-49,51]
4. The limited follow up time, some studies had long median follow up time but the minimum range of follow up was short. [24,40,41,43,44,46,48-49]
5. not adjust for other prognostic factors.[40,45,47]

Moreover, the criteria to interpret the positive bcl-2 staining are different in these studies (Table 2.3). It seems that if the positive criteria is set at more than 5% of tumor cells with positive stain, the prevalence of bcl-2 positive cervical cancer is around 60% and bcl-2 seems to be of prognostic significance.[25,41,42,44]

Table 2.3 Various studies that evaluated the relationship between bcl-2 expression and prognosis in invasive cervical cancer.

Authors Year	Stage	Treatment	Number of patients	Criteria for positive bcl-2	Positive bcl –2 (%)	Follow up Median (range)
Studies which demonstrated that bcl-2 expression was associated with longer survival						
Tjalma[25] 1997	Ia-IIb	Surg 41% adj RT	76	> 5%	63	39 mo (4-203 mo)
Crawford[40] 1998	I-IV	NA	44	> 10%	34	35 mo (1-74 mo)
Tjalma[41] 1998	I-IV	Surg, RT, chemo	137	> 5%	61	NA
Padovan[42] 2000	Ib-IVb	Surg 62% adj Rx	86	> 5%	60.5	All 10 years
Dimitrakakis[43] 2000	Ib-IIa	Surg alone	81	> 10%	28.4	45 mo (3-125 mo)
Tjalma[44] 2001	Ia-IVb	NA	111	> 5%	68	50 mo (4-227 mo)
Studies which demonstrated that bcl-2 expression was associated with shorter survival						
Rajkumar[45] 1999	IIb-IIIb	RT	40	>0%?	65	5 yrs
Pillai[46] 1999	IIb-IIIb	RT	101	NA	NA	16 mo
Studies which could not demonstrate the association between bcl-2 expression and survival rate						
Uehara[47] 1995	Ib-IIb	Surg 25% adj RT	259	>0%	33	NA
Harima[48] 1998	Ib-IVb	RT	44	>30%	61	19 mo (1.7-40 mo)
Harima[49] 2000	IIIb	RT± hyperthermia	37	>10%	35	23 mo (1.7-40 mo)
Graflund[50] 2002	Ib-IIb	Surg ± adj Rx	168	>30%	43.5	222 months (6-10 years)
Ozalp[51] 2002	Ib-IIb	Surg Unk adj Rx	28	>5%	54	NA
Jain[52] 2003	IIb-III	RT	76	>0%	38	5 years

NA - not available.

Surg =surgery, adj =adjuvant , RT=radiotherapy, chemo=chemotherapy, Unk=unknown

Rx=treatment=radiotherapy and/or chemotherapy.

2.3 Prognostic significance of bcl-2 in cervical cancer treated by surgery

From the literature review about the prognostic significance of bcl-2 in cervical cancer patients primarily treated by surgery, only one study[43] evaluated the patients treated solely by surgery, 4 studies[25,42,47,51] included patients treated with or without postoperative adjuvant radiotherapy or chemotherapy while another study[50] did not clarify about adjuvant postoperative treatment.

In 2000, Dimitrakakis et al[43] evaluated bcl-2 and p53 expression in 81 invasive cervical cancer stage Ib/IIa treated by radical hysterectomy without preoperative or postoperative adjuvant treatment. Similar rates of bcl-2 expression were seen in cervical tumor subtypes [squamous cell carcinoma, 18/63 (29%) vs. adenocarcinoma, 5/18 (28%)]. Five-year survival rate of patients with positive bcl-2 was 73.9%, which was statistically significantly higher than 48.3% in those with negative bcl-2 ($p=0.02$). In multivariable analysis by Cox proportional hazards, lymph node metastasis ($p<0.001$), tumor size ($p<0.001$), histological type ($p=0.05$), and bcl-2 expression ($p=0.04$) were found to be significant indicators of overall survival.

In 1995, Uehara et al[47] studied bcl-2 expression in 259 stage Ib-IIb cervical cancer. No chemotherapy or radiotherapy was given before surgery. Local radiotherapy was given to 64 patients later because of regional lymph nodes metastases. Bcl-2 protein positive was found in 33%. No significant difference in survival at five years was noted between bcl-2 negative (78%) and bcl-2 positive (82%) cases ($p=0.001$).

In 1997, Tjalma et al[25] evaluated bcl-2 expression in radical hysterectomy specimens from 76 patients with untreated stage Ia-IIb cervical cancer. Postoperatively, 25 patients with lymph node metastasis and 6 node negative patients with LVSI received adjuvant external field pelvic radiotherapy. A heterogeneous distribution of bcl-2 expression was observed in the neoplastic cells of the tumor. Forty-eight (63%) cervical carcinoma were bcl-2 positive. There was no significant association between bcl-2 expression and tumor histology, tumor differentiation, stage, presence of lymph node metastasis or LVSI. The five-year survival rate for patients with bcl-2 negative tumors was 34% and for bcl-2 positive ones was 71% ($p<0.001$). Subgroup analysis showed that both for lymph node negative ($p<0.001$), and lymph node positive groups ($p<0.001$), patients with bcl-2 positive tumors had a better prognosis. Multiple regression analysis adjusted for stage and LVSI also demonstrated a significantly shorter overall survival for patients with bcl-2 negative tumor.

In 2000, Padovan et al[42] studied bcl-2, p53 and Ki-67 in 86 invasive squamous cell carcinoma of the uterine cervix stage Ib-IVb. All patients underwent surgery as the first therapy; 84 by radical hysterectomy, 1 by pelvic exenteration and another underwent only exploratory laparotomy. Thirty-three patients did not undergo adjuvant therapy; 12 had chemotherapy, 34 radiotherapy and 7 both chemo- and radiotherapy. Fifty-two cases (60.4%) were positive for bcl-2. The majority of stage Ib was bcl-2 positive (87.2%). On the contrary, all cases in stage IV were negative for bcl-2. There were no significant differences in the marker for stages II (52.9%) and III (36%). In comparison with p53 and Ki67, bcl-2 expression was the most significant prognostic factor for longer survival ($p=0.002$).

In 2002, Graflund et al[50] studied bcl-2 in 168 invasive cervical cancer stage Ia-IIb treated by radical hysterectomy. Adjuvant radiotherapy was administered in cases with lymph node metastasis, parametrial involvement, or marked LVSI. Bcl-2 positive was found in 43.5%. There was no significant association between the expression of bcl-2 protein and the age of the patients or the FIGO substage of the tumors. Tumor histopathology and grade were not associated with bcl-2 staining. The bcl-2 status of the tumors did not predict the presence of pelvic lymph node metastasis, tumor recurrences, or tumor-related death.

In 2002, Ozalp et al[51] evaluated bcl-2 in 28 invasive cervical cancer stage I-IIb treated by radical hysterectomy. Bcl-2 expression was positive in 54%. The mean overall survival in bcl-2 positive was 48.5 months compared to 56.7 months in bcl-2 negative, which was not statistically significant difference.