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A review of prognostic factors in early-stage carcinoma of the cervix (FIGO I B and II A) and implications for treatment strategy

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Summary

Several prognostic factors in stages I B and II A cervical carcinoma have been widely studied to define groups of patients with a poor prognosis. Most of these factors are interrelated. The characteristics which should be regarded as main factors have not yet been defined, because the studies reported were based on mainly retrospective and non-randomized analysis. Reviewing the literature, lymph node metastasis, differentiation grade, tumor size, parametrial extension, lymph-blood vessel invasion and cervical invasion seem to be prognostically important factors, which suggests that the subdivision of patients according to the FIGO classification alone is inaccurate. It seems useful to define subgroups of patients according to tumor characteristics, determined after surgical treatment and accurate histologic examination of the surgical specimen. Patients with one or more of these tumor features need additional treatment to improve survival. The current treatment modalities, such as postoperative radiotherapy, have not been thoroughly evaluated, but doubt exists as to their efficacy. Data in the literature suggest that particularly patients with para-aortic or multiple pelvic lymph node metastasis (> 3) have already developed distant metastases at the time of primary treatment and therefore need adjuvant systemic therapy. Patients with tumors larger than 4 cm in diameter, differentiation grade III, lymph-blood vessel invasion or cervical invasion (of more than 70%) seem to have high recurrence rates at both pelvic and distant sites, indicating that there is also a need for better pelvic control.

Carcinoma, early-stage; Prognostic factor; Improved survival

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Introduction

Early-stage carcinoma of the cervix is associated with a good prognosis. Five-year survival rates of stages I B and II A are 80–90% and 70–80% respectively. In several large series, stages I B and II A have been evaluated together and 5-year survival rates of approximately 80% were reported. Patients are staged by the FIGO clinical classification. Stage I B and II A, in which there is no clinical infiltration of the parametria, can both be treated by either surgical or radiation therapy. The results obtained using these methods are comparable, there being no difference in morbidity and mortality [16,36,39,47,90,97].

Still, about 20% of stage I B or II A patients die of cervical cancer and this has not changed in the past two decades. Several observations have suggested that treatment failure in this 20% may be attributed to the inadequacy of localized therapy when certain morphologic and histologic tumor features exist. The problem for the oncologist is to define these subsets of patients and seek more appropriate treatment modalities.

This paper reviews the prognostic factors which have been identified in early-stage carcinoma and discusses possible modifications of treatment for improving survival.

Prognostic factors

Lymph node metastases

Involvement of lymph nodes is probably one of the most important prognostic factors. The incidence of positive pelvic lymph nodes reported in the medical literature in stage I B and II A varied between 4 and 34%, with a mean of 17%. Much lower incidences of common iliac and para-aortic lymph node involvement, 3% and 5% respectively, have been found in these patient groups (Table I).

Analysis of recurrence sites demonstrated a slightly higher incidence of distant recurrence, with or without local recurrence when pelvic nodes were involved, namely 27% versus 16% local recurrences. In patients with positive para-aortic lymph nodes there is a high incidence (44%) of distant recurrence, with or without local recurrence (Table II).

Patients with pelvic lymph node metastases had 5-year survival rates as low as 38% and as high as 62%. In general, there is a fall in overall 5-year survival rate of approximately 50% when pelvic lymph nodes are involved (Table III). The number and degree of involvement of positive nodes have an additional detrimental influence on prognosis [30,47,65,127]. Inoue et al. [64] reported a 5-year survival of only 22% of 9 patients with more than 3 positive pelvic lymph nodes. A 5-year survival rate of 31% was found by Pilleron et al. [109] in 26 patients with more than 20% of the lymph nodes removed positive. Unfortunately, there has been little documented about survival rates of early-stage patients with common iliac or para-aortic node metastases. Pilleron et al. [109] noted a 5-year survival rate of only 16% of patients with positive common iliac nodes in stages I and II. In advanced stages, 5-year survival rates of patients with para-aortic disease ranging from 16 to 32% have been described, illustrating the bleak prognosis [3,11,63,112,115].

TABLE I

Incidence of lymph node metastasis according to the highest level in stage I B and/or II A (FIGO)

Site	Number of patients [a]		References
	Total	Positive nodes	
Pelvic	70	3 (4)	62
	195	18 (9)	2
	194	19 (10)	61
	108	11 (10)	79
	362	47 (13)	64
	139	20 (14)	16
	418	62 (15)	47
	124	22 (18)	19
	98	19 (19)	30
	363	73 (20)	70
	193	42 (22)	127
	143	35 (24)	76
	293	71 (24)	71
	145	39 (27)	110
	63	19 (30)	89
	73	25 (34)	24
Common iliac	363	8 (2)	70
	193	4 (2)	127
	98	3 (3)	30
	202	5 (3)	60
	293	20 (7)	71
Para-aortic	98	3 (3)	30
	140	6 (4)	63
	254	9 (4)	99
	171	9 (5)	47
	143	8 (6)	76
	183	11 (6)	11
	51	5 (10)	8

[a] Figures in parenthesis denote percentages.

Histology: cell differentiation and cell type

The relationship between grade of cell differentiation of cervical cancer and survival has been the subject of numerous publications. In some studies tumors were subdivided into four grades of differentiation according to Broders [88,133]. Recent investigations distinguished three grades of differentiation, in which grades three and four are combined. Several authors reported a significantly better 5-year survival rate with well-differentiated lesions (grade I) in comparison with poorly differentiated tumors (grade III) (Table IV). In addition, a positive correlation with stage and rate of lymph node metastases and recurrences has been described [1,5,8,47,133]. Chung et al. [31] noted in their retrospective analysis a significantly higher incidence of lymph node metastases and tumor recurrences in patients with poorly differentiated tumors (grade III) than in those with well or moderately

TABLE II

Incidence and site of first recurrence in relation to the highest level of positive lymph nodes

Site	Number of patients [a]			References
	Total	Pelvic recurrence only	Distant metastases with or without pelvic recurrence	
Pelvic	97	15 (16)	24 (25)	97
	19	3 (16)	3 (16)	30
	42	6 (14)	13 (31)	127
	125	34 (27)	34 (27)	67
	143	10 (7)	42 (29)	64
Para-aortic and/or common iliac	36		27 (75)	138
	23		12 (52)	96
	23		8 (35)	21
	31		17 (54)	136
	79	13 (17)	25 (32)	115
	98	25 (26)	40 (41)	11

[a] Figures in parenthesis denote percentages.

differentiated lesions (grade I–II), namely 53% versus 17% and 20% versus 6%, respectively.

There is no consensus concerning the significance of cell type. Martzloff proposed classification into keratinizing, non-keratinizing, large cell and parvocellular carcinomas. According to Wentz and Reagan [31] and Van Nagell et al. [93,95] parvocellular carcinomas are regarded as prognostically unfavourable. Pejovic et al. [103], Fuller et al. [47] and Kortmeier [73] described a better prognosis for patients with squamous cell carcinoma than for patients with adenocarcinoma. Others

TABLE III

Five-year survival rate of patients in stage I B and/or II A (FIGO), positive versus negative pelvic lymph nodes

Authors	Total No. of patients	No. with negative nodes	% 5-year survival	No. with positive nodes	% 5-year survival
Liu and Meigs, 1955 [80]	116	95	82.0	21	38.0
Brunschwig, 1960 [19]	138	116	88.0	22	50.0
Christensen et al., 1964 [29]	167	139	92.0	28	39.3
Brunschwig and Barber, 1966 [20]	273	235	83.4	38	50.0
Newton, 1975 [97]	58	53	91.3	5	40.0
Morley and Seski, 1976 [90]	143	125	96.0	18	55.6
Boyce et al., 1981 [16]	139	119	91.0	20	62.0
Ketting et al., 1981 [70]	185	166	91.4	19	42.1
Baltzer et al., 1982 [5]	718	–	88.4	–	54.0
Timmer, 1982 [127]	193	151	94.0	42	37.0
Ireland et al., 1985 [66]	48	34	91.1	14	50.0

TABLE IV

Five-year survival rate in relation to cell differentiation grade in stage I B and/or II A (FIGO)

Differentiation grade	References					
	5		8		66	
	No. of patients	% 5-year survival	No. of patients	% 5-year survival	No. of patients	% 5-year survival
I	119	85	19	84	21	95
II	407	80	18	78	6	83
III	192	72	14	50	18	39

[7,13,16,30,98], however, found no cell-type dependent differences in prognosis. Swan et al. [124] found a better survival rate with large non-keratinizing carcinomas compared with parvocellular carcinomas after radiotherapy, but not after surgical treatment, suggesting that parvocellular carcinomas are less radiosensitive.

In summary, it is still doubtful whether cell type is of prognostic significance.

Tumor size

The prognostic significance of tumor size has been pointed out by several authors. Although different criteria concerning tumor size have been used in the literature, it might be concluded that increasing tumor size is associated with an increased incidence of lymph node metastases, recurrences and decreased 5-year survival (Table V).

TABLE V

Incidence of lymph node metastasis, recurrence and five-year survival rate in relation to tumor size in stage I B and/or II A (FIGO)

Total No. of patients	Tumor size	No. of patients	% nodes positive	% recurrences	% 5-year survival rate	References
82	< 2 cm	46	9	–	91	93
	⩾ 2 cm	36	31	–	69	
135	< 2 cm	85	6	5	–	95
	⩾ 2 cm	50	18	24	–	
48	< 3 cm	35	20	–	–	66
	⩾ 3 cm	13	40	–	–	
123	< 3 cm	74	–	–	90	110
	⩾ 3 cm	49	–	–	65	
98	< 4 cm	83	16	5	92 [a]	30
	⩾ 4 cm	15	80	80	47 [a]	
122	< 4 cm	103	–	10	–	31
	⩾ 4 cm	19	–	58	–	

[a] Two-year survival rate.

Unfortunately, data on methods of tumor measurement have rarely been given in the literature. Most authors measured tumor size by clinical examination at the time of pre-therapeutic staging. Only a few reports gave details on tumor measurement by standardized histological work-up of the removed uterus and parametria [4,5,18,88]. The latter procedure is more accurate, but only possible when surgery is the primary treatment. Baltzer et al. [4,5], for instance, measured the tumor volume of the removed specimen very accurately. In a study of 595 patients they found 17% lymph node metastases when tumor volume was less than 6500 nm and 46% when tumor volume was more than 6500 nm. They also found a significantly reduced 5-year survival rate with increasing tumor volume. Whereas the 5-year survival rate of these patients with a tumor volume of 500–1500 mm^3 was 84.2%, the 5-year survival rate fell to 75% with a tumor volume of 6500–10 000 mm^3 and to 59.5% with a volume over 20 000 mm^3.

Parametrial extension

Although parametria appeared to be tumor-free at the time of pretherapeutic staging (FIGO), in some cases parametrial extension was found after histologic examination of the surgical specimen.

Involvement of the parametrial tissue significantly influences the results of treatment. Reported incidences of parametrial extension in early stages varied between 7% and 16.8% [13,60,64]. There is a good correlation between parametrial extension and the incidence of lymph node metastases and recurrence [13,16,60,64,82,98]. A significant difference in 5-year survival rate has been described between patients with and without parametrial extension (Table VI).

Lymph and blood vessel invasion

Because it is difficult to distinguish between tumor invasion into lymph and blood vessels, reports in the literature are rare and great variation in incidence (21–50%) has been reported [43,119].

Positive correlations with incidence of lymph node metastases and recurrences have been reported in the literature [5,16,25,30,44,94,95]. There is also a vast range in 5-year survival rates of patients with lymph-blood vessel invasion (Table VII). Some authors have evaluated these factors separately, and found incidences of lymphangiosis carcinomatosa of 39–57% and incidences of blood vessel invasion of 2–29% [5,25,43,44,52]. Survival was especially poor when blood vessels were invaded; 5-year survival rate was 21–50% (Table VIII).

TABLE VI

Five-year survival rate in relation to parametrial extension (PE) in stage I B and/or II A (FIGO)

Total No. of patients	No. of patients – PE	% 5-year survival	No. of patients + PE	% 5-year survival	References
110	99	95	11	60	16
305	277	90	28	75	13
307	291	97	16	81	64

TABLE VII

Five-year survival rate in relation to lymph-blood vessel invasion (LBI) in stage I B and/or II A (FIGO)

Total No. of patients	No. of patients – LBI	% 5-year survival	No. of patients + LBI	% 5-year survival	References
66	37	65	29	21	43
68	48	79	20	50	44
42	28	88	14	54	52
84	51	90	33	60	6
139	98	96	41	70	16
718	310	90	408	68	5

TABLE VIII

Five-year survival rate in relation to blood vessel invasion (BI) in stage I B and/or II A (FIGO)

Total No. of Patients	No. of patients – BI	% 5-year survival	No. of patients + BI	% 5-year survival	References
66	37	65	29	21	43
68	48	79	20	50	44
718	648	83	69	30	5

Cervical invasion

Chung et al. [30] were one of the first to describe the importance of cervical invasion in prognosis and noted a significantly increased frequency of positive lymph nodes, recurrences and reduced 2-year survival rates when depth of cervical

TABLE IX

Incidence of lymph node metastasis, recurrence and 5-year survival rates in relation to depth of cervical invasion in stage I B and/or II A (FIGO)

Total No. of patients	Depth of cervical invasion	No. of patients	% node positive	% recurrences	% 5-year survival	References
684	< 10 mm	–	11	–	–	4
	> 10 mm	–	27	–	–	
51	< 10 mm	43	14	–	79	8
	> 10 mm	8	50	–	50	
136	< 10 mm	89	–	5	96	16
	> 10 mm	47	–	34	70	
150	< 50%	129	–	–	88	133
	> 50%	21	–	–	80	
85	< 50%	70	13	4	93 [a]	30
	> 50%	15	40	40	67 [a]	

[a] Two-year survival rate.

invasion was more than 70%. Many other authors, although using different selection criteria, also reported good correlation between the depth of cervical invasion and the incidence of lymph node metastasis, recurrence and 5-year survival rate (Table IX).

Only Underwood et al. [133] found no significant differences in survival rates between cervical invasion of greater or less than 50%.

Other possible prognostic factors

Age and hormonal status have been mentioned as prognostic factors, although reported conclusions were not unanimous [40,88,103,123]. According to Boyce et al. [16], Noguchi et al. [98], Rotman et al. [119] and Perez et al. [105] patients with tumor extension to the corpus uteri or vagina have a high risk of treatment failure.

Lymphatic cell infiltration in stroma has been found to be of prognostic importance by some authors [5,49,4], although Noguchi et al. [98] could not demonstrate a relationship between survival and stromal infiltration. Baltzer et al. [5] noted that the morphology of the tumor was of importance with regard to prognosis. Various reports have suggested that endocervical tumors are related to an increased rate of local recurrence and consequently have poorer survival rates [1,47,48,95,101,119].

In 1947 Graham showed a correlation between tumor regression after radiotherapy and treatment outcome. This observation has been confirmed, suggesting that there are differences in the radiosensitivity of cervical carcinomas [52,58,88].

Discussion

The main prognostic factors

Various factors related to prognosis have been studied, but the question of which prognostic factor should be regarded as the most important has not been answered.

Reviewing mainly retrospective data in the literature, lymph node metastases, differentiation grade, tumor size, parametrial extension, lymph-blood vessel invasion and cervical invasion appear to allow prediction of survival. The relative importance of any single factor is difficult to determine without a multivariate analysis, because most of the prognostic factors are interrelated. A combination of certain factors apparently has a worse prognosis than those factors separately. Bleker et al. [13] and Inoue [64], for example, found a significantly lower survival rate in patients with parametrial extension and lymph node metastases together when compared to patients in whom only one of these factors was present. The first author noted a 5-year survival rate of 50% if parametrial extension and lymph nodes were positive. These figures increased to 62.1% if only positive lymph nodes were found, and to 75% if only parametrial extension was diagnosed. The survival rate was 90.3% when none of these factors was present. The second author reported that parametrial invasion and lymph node involvement combined reveals a 5-year survival rate of 42.5%, rising to 73.3% in cases of positive lymph nodes only, and to 69.6% in cases with parametrial invasion only. Patients without these factors had a survival rate of 97.3%. Fuller et al. [47] described the added detrimental effect of

increased tumor size, lymph-blood vessel invasion and deep cervical invasion on the prognosis of patients with lymph node metastases.

This survey suggests that the FIGO classification, which is based on clinical examination, is inaccurate for subdividing groups of patients for therapy and prognosis. Patient selection according to the tumor characteristics, as discussed in this article, is more accurate, but is possible only by careful standardized examination of the surgical specimen after surgical treatment. Modifications of standard treatment on the basis of pathologic parameters have been suggested by several other authors [5,16,47,49,95,119,139].

Site of recurrence in relation to prognostic factors

Besides prognostic considerations, the site of recurrence is also important with regard to alterations in conventional treatment. Not only the high risk of recurrence but also knowledge of the site of recurrence is essential for interpretation of the need for additional therapy. The high incidence of distant recurrence and the relatively low incidence of pelvic recurrence in patients treated with surgery, radiotherapy or a combination of these methods indicates that locoregional therapy is insufficient. It suggests that patients could benefit more from systemic therapy.

Analysis of recurrence sites in relation to prognostic factors has rarely been performed, although some retrospective analyses have been reported. It has already been pointed out in this review that pelvic lymph node metastasis is associated with distant recurrence, with or without pelvic recurrences, in 16–31% of patients. Incidences of only pelvic recurrences in this group range from 7% to 27%. The number and the degree of node involvement seem to increase the risk of distant metastases. Large positive pelvic nodes (> 20 mm) were highly correlated with more than three positive pelvic nodes according to Inoue et al. [65]. Chung et al. [30] found an incidence of 70% distant metastasis with grossly positive pelvic nodes.

Although blood vessel invasion is associated with a high recurrence rate (up to 70%) and a poor prognosis, there are no exact figures concerning the recurrence sites. With combined lymph-blood vessel invasion, 23–25% distant recurrences and 13–20% pelvic recurrences have been reported [30,94]. These data allow no conclusions concerning the risk of distant recurrence in relation to invasion of blood vessels alone.

Patients with tumors larger than 4 cm had 14–40% incidence of distant recurrences and 9–40% incidence of pelvic recurrences [30,48].

Incidences of distant and pelvic recurrences of 20% and 25% respectively have been reported in relation to differentiation grade III [31]. These findings indicate that large tumors (> 4 cm) and poor differentiation (grade III) increase the risk of pelvic recurrences as much as for distant recurrences.

Chung et al. [30] found a higher incidence of pelvic recurrences than of distant recurrences, 27% versus 13%, when cervical invasion was more than 70%.

In summary, there are some indications that patients with para-aortic and multiple (> 3) pelvic lymph node metastases have higher incidences of distant recurrences than of pelvic recurrences. Unfortunately there are too few data to indicate the recurrence sites of patients with blood vessel invasion, differentiation

grade III, large tumors and deep cervical invasion, but the incidence of recurrence at both pelvic and distant sites is high. However, so far there have been no studies in the literature that prove that this hypothesis is correct.

The impact of treatment

One of the questions to be answered is whether there are possible therapy modifications for improvement of survival of patients with one or more poor prognostic features. The efficacy of the current radiotherapeutic treatment strategies is not well defined for every subgroup.

A study by Lagasse et al. [74] suggested that radiotherapy with a dose of 5000 rad could sterilize undetected pelvic tumor residues in operated stage I B and II A patients. They found in a prospective randomized analysis of 118 stage I B patients an apparent decrease (from 22.4% to 11.7%) in the incidence of observed pelvic node involvement after radiation therapy. According to these findings postoperative radiotherapy might benefit high-risk patients also. Postoperative pelvic radiation for patients with lymph node metastases and parametrial extension of lymph-blood vessel invasion has been investigated in several studies. Some authors reported a slightly improved survival rate [41,53,68,86], but the majority [13,16,30,47,60,91, 120,139] did not find a better survival rate with this additional treatment. Unfortunately all these studies were retrospective and used non-randomized analysis. However, according to these studies it might be concluded that the effectiveness of postoperative pelvic radiotherapy is still doubtful. A possible explanation for this lack of response is that the presence of these prognostic factors may not represent the anatomical spread of disease but rather may be associated with undetected extrapelvic metastases. This hypothesis is supported by some studies [8,47,60,127]. Postoperative radiated patients had fewer pelvic recurrences but more extrapelvic recurrences in comparison with non-radiated patients. Extensive randomized prospective studies are still necessary to evaluate this additional treatment.

The value of applying para-aortic radiation in early-stage carcinoma of the cervix with para-aortic lymph node metastases is still unknown. Extended-field radiation has been used more in advanced stages, because in these stages there is a relatively high incidence of para-aortic node involvement, 17–35% [3,11,37,63,76,131,136]. However, there also seems to be a high incidence of para-aortic disease in high-risk patients in early stages [63,75,136]. Early-stage patients with tumors of more than 4 cm, blood vessel invasion, or para-aortic or multiple (> 3) pelvic lymph node metastases appeared to have survival rates which are comparable with those in advanced stages. This suggests the need for investigation of the effectiveness of adjuvant treatment in this patient group. In advanced stages some patients with biopsy-proven para-aortic disease have been cured with extended-field radiotherapy. Five-year survival rates of 9.6–29% have been reported. The majority still died from recurrent disease. Analysis of sites of recurrences in patients with positive para-aortic nodes suggests that many develop para-aortic and distant metastases simultaneously (Table II). In addition, extended-field radiation is associated with a high risk of severe complications [3,11,27,37,115]. In reports of systemic therapy, *cis*-platinum is the best-documented agent showing activity. Response rates with this cytotoxic

agent in advanced recurrent carcinomas vary between 30 and 70% [22,23,34,45,118, 122,125,126], with preference for the lower response rates. This variation in response rates is due to different risk factors in patient populations and different criteria in determining the response. Combination chemotherapy of *cis*-platinum and other active drugs results in comparable response rates. Theoretically, in patients with occult distant micro-metastases it may be possible to eliminate micro-metastases by chemotherapy alone.

Conclusions

The current knowledge of prognostic factors and sites of recurrence is based mainly on retrospective studies. The literature indicates that lymph node metastasis, differentiation grade, tumor size, parametrial extension, lymph-blood vessel invasion and cervical invasion seem to be of prognostic importance in stage I B and II A carcinoma. The relative importance of any single factor is difficult to determine without a multivariate analysis because most of the prognostic reactors are interrelated.

According to the findings mentioned before, it appears that the current treatment is insufficient to improve survival of high-risk patients. Improvement in survival with para-aortic or multiple (> 3) pelvic lymph node metastases can mainly be established by the development of an effective systemic treatment. Patients with blood vessel invasion, tumors of more than 4 cm diameter, differentiation grade III, or cervical invasion of more than 70% could also benefit from systemic treatment. However, better pelvic controls seems to be important as well with these factors.

Refined radiotherapeutic treatment is necessary to improve control at the pelvic site. Recently developed modalities such as radiation sensitizers and protectors, hyperthermia or high LET particles seems promising [17,106,113,119].

A further improvement in treatment of patients with early stages of cervical cancer and at risk for distant metastasis may be provided by adjuvant chemotherapy to eliminate those micrometastases outside the pelvis.

The findings concerning prognostic variables indicate that the FIGO classification alone, which is based on clinical examination, is an inaccurate basis on which to subdivide patients with regard to treatment and prognosis. It seems useful to define subgroups of patients according to the characteristics of the tumor defined after surgical treatment and accurate pathological examination of the surgical specimen.

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