Evaluation of treatment results and prognostic factors in early-stage cervical carcinoma patients treated with postoperative radiotherapy or radiochemotherapy

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Summary

Purpose: To investigate the clinical features, prognostic factors, and treatment outcome in early-stage cervical carcinoma patients treated with postoperative radiotherapy (RT)/radiochemotherapy (RCT). *Methods:* The records of 256 Stage IB and II cervical cancer patients treated with postoperative RT/RCT from 1992-2007 were retrospectively reviewed. Median age of the patients was 47 (range: 25-78). Two hundred one (78.6%) patients had squamous cell carcinoma and 29 (11.3%) had adenocarcinoma. One hundred and eighty-seven (73.0%) had FIGO Stage IB and 69 (27%) had Stage II disease. Concomitant cisplatin-based chemotherapy was administered to 47 (18.4%) patients. Metastatic lymph node ratio (MLNR), defined as number of metastatic lymph nodes divided by the number of dissected lymph nodes, was 0 in 142 (55.5%) patients, from 1% to 10% in 27 (10.5%) and > 10% in 31 (12.1%) patients. *Results:* Median follow-up duration was 60.5 months (range: 6-202 months). Five-year locoregional control (LRC), disease-free survival (DFS), disease specific survival (DSS) and overall survival (OS) rates were 90.8%, 83.4%, 91.2%, and 85%, respectively. In multivariate analysis; bulky tumor (> 4 cm) was shown as an important prognostic factor for LRC, DFS and DSS. Pretreatment hemoglobin level (< 10 g/dl) was associated with lower OS rate. Endometrial involvement was associated with lower LRC and DFS. Treatment break > 14 days showed significance for DFS and DSS. MLNR was found as a valuable prognostic factor for all endpoints (LRC, DFS, DSS and OS). The rate of grade 3-4 late toxicity was 3.6% and 2%, respectively. *Conclusion:* Postoperative RT/RCT is an effective treatment modality for early-stage cervical cancer patients with unfavorable features and provides satisfactory local control and survival rates with low morbidity.

Key words: Cervical cancer; Radiotherapy; Radiochemotherapy; Prognostic factors; Metastatic lymph node ratio; Side-effects.

Introduction

Patients with early-stage cervical cancer (FIGO Stage IB and IIA) can be effectively treated with either radical surgery or radiotherapy (RT). Five-year overall and progression-free survival rates are comparable in both treatment modalities but treatment associated morbidity may differ [1]. Genitourinary symptoms are more commonly seen in the surgery group, whereas gastrointestinal symptoms are more common in patients selected to undergo RT or radiochemotherapy (RCT). The choice of treatment modality depends on institution experience, the gynecologic oncologist or radiation oncologist preference, patient general health, age and characteristics of the lesion [2].

With external beam RT and brachytherapy, the 5-year survival rate is 86-92% for Stage IB, 75% for Stage IIA and 60% for Stage IIB disease. The overall pelvic failure rate in Stage IB is approximately 5% to 8%, and 15-20% in Stage IIA disease [2].

Several clinical and histopathologic unfavorable features (lymph node metastases, parametrial invasion, positive surgical margin) have been shown to increase the pelvic recurrence and distant metastasis rates for patients treated surgically. In this group of patients the addition of postoperative adjuvant RT/RCT has demonstrated improved outcomes [3-5]. Combined treatment modality (radical surgery followed by RT/RCT) comes with a price for the patient – an increased incidence of side-effects. For patients who undergo combined treatment modality lymphedema risk increases up to 30% and enteric complications to 20-24% [6, 7].

The aim of this study was to investigate the clinical and histological features, prognostic factors, and treatment results in early-stage cervical carcinoma patients treated with postoperative RT/RCT at a single institution over a 16-year period.

Materials and Methods

Patients

From January 1992 to December 2007, 256 cervical cancer patients treated with postoperative RT/RCT at Ege University Faculty of Medicine, Department of Radiation Oncology were retrospectively reviewed. Patients with at least six months of follow-up were included in this analysis. Median age of the patients was 47 years (range: 25-78).

The histology was squamous cell carcinoma in 201 (78.6%), adenocarcinoma in 29 (11.3%), adenosquamous cell carcinoma

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in ten (3.3%), and other in 16 (6.3%). All patients were staged according to FIGO staging system. Preoperative examination consisted of a medical history, complete blood count and biochemical tests, clinical examination under general anesthesia, chest X-ray, and abdominopelvic ultrasound (US). In case of suspicious findings in X-ray or US, computerized tomography (CT) of the thorax, abdomen and/or pelvis was performed.

One hundred and thirty-five (52.7%) patients had FIGO Stage IB1, 52 (20.3%) had Stage IB2, 35 (13.7%) had Stage IIA, and 34 (13.3%) had Stage IIB disease. The type of surgical procedure was as follows: Wertheim operation in 175 (68.4%) patients, total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAH+BSO) +lymphadenectomy in 45 (17.6%), and suboptimal surgery (TAH+BSO/total abdominal hysterectomy with a unilateral salpingo-oophorectomy (TAH+USO)/TAH) in 36 (14%) patients. Median and mean number of removed lymph nodes were 20 and 23, respectively (range: 1-95). Median and mean number of metastatic lymph nodes was two (range: 1-15) for both. Metastatic lymph node ratio (MLNR) was defined as number of metastatic lymph nodes divided by the number of dissected lymph nodes. MLNR was evaluated in three categories (0; 1-10%; >10%) and respectively, 142 (55.5%), 27 (10.5%) and 31 (12.1%) patients were in each group. In 56 (21.9%) patients, we were unable to determine MLNR due to the lack of lymphadenectomy and/or the lack of information of number of retrieved lymph nodes in the pathology reports.

Surgical margin was positive in 24 (9.4%), parametrial invasion was present in 34 (13.3%) and endometrial extension was present in 26 (10.2%) patients. Lymphovascular space invasion (LVSI) was detected in 82 (32%) patients. The median pretreatment hemoglobin (Hb) level was 12.5 g/dl (range: 8.5-15.1). Patient and treatment-related characteristics are shown in Table 1.

Table 1. — *Patient and disease characteristics*.

Characteristics	N (%)
Median age: 47 (Range: 25-78)	
Menopausal status	
Premenopausal	110 (43)
Perimenopausal	20 (7.8)
Postmenopausal	126 (49.2)
FIGO stage	
IB1	135 (52.7)
IB2	52 (20.3)
IIA	35 (13.7)
IIB	34 (13.3)
Surgery	
Wertheim	175 (68.4)
TAH+BSO+lymphadenectomy	45 (17.6)
Suboptimal (TAH+BSO/TAH+USO/TAH/ other types of surgery)	36 (14)
LVSI	
Absent	174 (67.9)
Present	82 (32)
Surgical margin	
Negative	232 (90.6)
Positive	24 (9.4)
Concurrent chemotherapy	
No	209 (81.6)
Yes	47 (18.4)
Parametrial invasion	
No	222 (86.7)
Yes	34 (13.3)
MLNR	
0	142 (55.5)
1-10%	27 (10.5)
> 10%	31 (12.1)
Undetermined	56 (21.9)
Endometrial involvement	
No	230 (89.9)
Yes	26 (10.2)

LVSI: Lymphovasculary space invasion; TAH: Total abdominal hysterectomy; BSO: Bilateral salpingooopherectomy; MLNR: Metastatic lymph node ratio.

Treatment

Postoperative RCT was applied in patients with lymph node metastases, positive/close surgical margin, bulky tumor (> 4 cm), and parametrial involvement, whereas postoperative RT was applied to patients with suboptimal surgery and/or with LVSI. Weekly concomitant cisplatin with the dose of 40 mg/m2 was administered to patients after 1999 and 47 (18.4%) patients received concomitant chemotherapy with RT. RT consisted of external RT and intracavitary brachytherapy in 236 (92.2%), and only external RT in 20 (7.8%) patients. External RT was applied with Co 60 teletherapy unit until the end of 1993 to 38 (14.8%) patients and with 6-18 MV linear accelerators to the rest of the patients thereafter. External RT was applied with 1.8 Gy daily fractions with a median total dose of 54 Gy (45-59.4 Gy). Radiotherapy portals were designed above the L5 vertebrae and below the obturator foramina for the initial phase up to 45 Gy or 50.4 Gy. For patients with positive surgical margins and metastatic pelvic lymph nodes external RT dose was escalated to 54 Gy. Brachytherapy was applied with high-dose rate afterloader (HDR) microselectron device to 0.5 cm depth from mucosal surface. Brachytherapy dose and fractionation changed during years (1 x 925 cGy from 1992 to 2000 and 3 x 600 cGy from 2000 to present).

Follow-up

Patients were followed with physical and gynecological examination, pap smear, and laboratory tests at 3-month intervals for the first two years, at 6-month intervals for three years, and annually thereafter. Acute and late toxicity was graded according to the Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer (RTOG/EORTC) toxicity criteria [8]. For survival endpoints – locoregional control (LRC), disease-free survival (DFS), disease-specific survival (DSS), and overall survival (OS) – time interval was defined as the time from surgery to the date of first relapse, disease-specific death or any death.

Statistical analyses

Statistical analyses were performed by Statistical Package for Social Sciences (SPSS) for Windows version 13.0 (SPSS Inc, Chicago, IL). Failure free and overall survival rates were estimated using the Kaplan Meier method, and patient and treatment groups were compared using the log-rank test. Multivariate analyses were performed with Cox proportional hazard models to test the differences between groups. All statistical tests were two-tailed with a significance level of 0.05.

Results

Median follow-up time was 60.5 months (range: 6-202 months). Five-year LRC, DFS, DSS and OS rates were 90.8%, 83.4%, 91.2%, and 85%, respectively. There were 39 (15.2%) patients with failures, of whom 17 had isolated locoregional failure, six had locoregional and distant failure, and 16 had distant failure. The location of isolated locoregional failures was as follows: cervical

stump in six, pelvic nodes in five, cervical stump+pelvic nodes in one, pelvic side wall in two and other in three. The median time for locoregional failure was 24 months (range: 4-90 months) and 35 months (range: 7-168 months) for distant metastases. The distribution of treatment related acute and late toxicity is indicated in Table 2.

Table 2. — *Distribution of acute and late term RT-induced toxicities*.

	Acute n (%)	Late n (%)
Gastrointestinal		
Grade 1	17 (14.4)	43 (16.8)
Grade 2	76 (29.7)	7 (2.7)
Grade 3	–	3 (1.2)
Grade 4	–	5 (2)
Genitourinary		
Grade 1	22 (8.6)	22 (8.6)
Grade 2	75 (29.3)	25 (9.8)
Grade 3	4 (1.6)	4 (1.6)
Grade 4	–	–
Skin		
Grade 1	24 (9.4)	25 (9.8)
Grade 2	22 (8.6)	21 (8.2)
Grade 3	3 (1.2)	2 (0.8)
Grade 4	–	–

GI: gastrointestinal system; GU: genitourinary system.

Univariate analysis

Significant prognostic factors for LRC were the presence of LVSI ($p = 0.03$), tumor size > 4 cm ($p = 0.01$), the presence of endometrial involvement ($p = 0.008$), and higher MLNR ($p < 0.001$). There was a trend for poorer LRC for the presence of parametrial invasion ($p = 0.07$), positive surgical margin ($p = 0.09$), and treatment break > 14 days ($p = 0.09$).

Similarly significant prognostic factors for DFS were tumor size > 4 cm ($p = 0.001$), parametrial invasion ($p = 0.04$), endometrial involvement ($p = 0.02$), treatment break > 14 days ($p = 0.006$) and higher MLNR ($p < 0.001$). There was a trend for poorer DFS, for pretreatment hemoglobin level ≤ 10 g/dl ($p = 0.06$), and positive surgical margin ($p = 0.08$).

For DSS; tumor size > 4 cm ($p = 0.01$), parametrial invasion (p=0.02), endometrial involvement ($p = 0.03$), positive surgical margin ($p = 0.02$), treatment break > 14 days ($p = 0.01$), and higher MLNR (p=0.001) were found as significant factors. For OS; older age ($p = 0.01$), advanced stage ($p = 0.03$), tumor size > 4 cm ($p = 0.005$), pretreatment Hb level ≤ 10 g/dl ($p = 0.02$), parametrial invasion ($p = 0.03$), and higher MLNR ($p = 0.001$) were found as significant factors. There was a trend for poorer OS in patients with positive surgical margin ($p = 0.06$) and treatment break > 14 days ($p = 0.09$).

The impact of median number of dissected LNs on local control and survival has been evaluated for patients ≤ 20 vs > 20 LNs removed and 5-year LRC (90.3% vs 93.7%, $p = 0.4$), for DFS (78.4% vs 89.8%, $p = 0.2$), for DSS (88.6% vs 92.8%, $p = 0.3$) and for OS (84% vs 83.9%, $p = 0.99$) respectively.

The influence of surgery type, optimal (Wertheim /TAH+BSO+lymphadenectomy) vs nonoptimal (TAH+BSO/TAH+USO/TAH) on the rates of local control and survival was evaluated. No significant difference was detected among patients treated with optimal vs non optimal surgery for LRC (91% vs 86%: $p = 0.6$), for DSS (90% vs 92%: $p = 0.8$), for DFS (83% vs 82%: $p = 0.9$) and for OS (84% vs 86%: $p = 0.3$), respectively. Five-year survival rates for these prognostic factors are listed in Table 3.

Multivariate analysis

Tumor size was shown as an important prognostic factor for LRC, DFS and DSS. Pretreatment Hb level (Hb ≤ 10 g/dl) was found to be a poor prognostic factor for OS. Endometrial involvement showed significance for LRC, and DFS. Treatment break (> 14 days) showed significance for DFS and DSS. MLNR was found as a valuable prognostic factor for all endpoints (LRC, DFS, DSS and OS). Univariate and multivariate analysis of prognostic factors is shown in Table 3.

Discussion

The current study evaluated the treatment results of FIGO Stage IB and II cervical cancer patients treated with postoperative RT/RCT at a single center within a period of 16 years. Five-year LRC, DFS, DSS and OS rates were 90.8%, 83.4%, 91.2%, and 85%, respectively which are consistent with several other series in the literature [9-13]. The only randomized trial assessing the benefit of postoperative RT in cervical cancer was the Gynecologic Oncology Group (GOG) 92 trial which evaluated early-stage cervical cancer patients without lymph node metastases, but was at a high risk of recurrence (bulky tumor, deep stromal invasion and LVSI). This study demonstrated that the addition of postoperative RT showed a 46% reduction in the risk of recurrence and a statistically significant reduction in the risk of progression or death [3].

For Stage I-IIA patients with lymph node metastases or positive margin or parametrial invasion, the addition of weekly cisplatin to postoperative RT was shown to improve progression free survival (80% vs 63%) and OS (81% vs 71%) [14]. Since the current study is a retrospective evaluation we can not assess the absolute benefit of RT or RCT on local control or survival. However the survival and toxicity rates of the patients treated with surgery followed by RT/RCT were satisfactory and similar to the other combined treatment modality study results in the published literature [9, 11].

Lymph node metastases have been shown to be an independent predictor and the most important prognostic factor for OS in cervical cancer patients [15, 16]. Five-year DFS rate was 57% in lymph node positive patients compared to 88% in lymph node negative patients [17]. Liu *et al*. analyzed 140 early-stage cervical cancer patients treated with surgery and postoperative RT and demonstrated that pelvic lymph node metastases was a

Table 3. — *Evaluation of prognostic factors affecting 5-year locoregional control, disease-free, disease-specific and overall survival rates.*

Prognostic factor	LRC %	univ.	multiv.	DFS %	univ.	multiv.	DSS %	univ.	multiv.	OS %	univ.	multiv.
Age (year)		0.27			0.16			0.16			**0.01**	0.06
≤ 47	93.1			86.1			92.7			89.5		
> 47	88.3			80			89.2			79.7		
Stage		0.11			0.14			0.1			**0.03**	0.94
IB1	94.9			88.5			94.7			90		
IB2	89.3			74.1			87.7			80		
IIA	83.2			83			91.9			82.6		
IIB	82.7			74.2			80.6			75.7		
LVSI		**0.03**	0.49		0.29			0.79			0.8	
Absent	94.3			85.4			91.5			86.2		
Present	84.9			79.7			90.5			82.3		
Tumor size		**0.01**	**0.04**		**0.001**	**0.001**		**0.01**	**0.003**		**0.005**	0.09
≤ 4 cm	95			90.2			92			88.7		
> 4 cm	84.4			61.6			77			70		
Hemoglobin g/dl		0.84			0.06			0.26			**0.02**	**0.01**
≤ 10	66.7			50			75			66.7		
> 10	90.8			82.9			91			97		
Parametrial invasion		0.07			**0.04**	0.4		**0.02**	0.15		**0.03**	0.87
No	91.9			84.8			92.8			86.5		
Yes	82.7			74.2			80.6			75.7		
Vaginal invasion		0.95			0.7			0.81			0.53	
No	90.8			83.5			91.6			85.1		
Yes	90.4			81.8			88			84.4		
Endometrial involvement		**0.008**	**0.003**		**0.02**	**0.03**		**0.03**	0.26		0.14	
No	93			85.6			92			86.2		
Yes	76.6			64.2			78.7			74.8		
Surgical margin		0.09			0.08			**0.02**	0.21		0.06	
Negative	91.8			84.5			92.8			87		
Positive	81.4			74			77.3			68		
Treatment break (days)		0.09			**0.006**	**0.001**		**0.01**	**0.002**		0.09	
≤ 14	91.2			84.7			91.9			86.5		
> 14	86.8			70.1			74.7			71.1		
MLNR		**0.000**	**0.01**		**0.000**	**0.001**		**0.001**	**0.01**		**0.001**	**0.005**
0	96.4			90.1			95.7			89.1		
1-10%	86.1			75.1			84.1			80.8		
>10%	76.1			62.8			73			63.5		
Histopathology		0.39			0.5			0.6			0.77	
Squamous cell carcinoma	90.5			84.5			91.7			87		
Adenocarcinoma	92.9			87.1			90.8			83.5		

AJCC: American Joint Comittee on Cancer; LVSI: Lymphovascular space invasion; MLNR: Metastatic lymph node ratio: RT: radiotherapy; LRC: Locoregional control; DFS: Disease free survival; DSS: disease specific survival; OS; Overall survival.

significant prognostic factor for DFS (77% vs 57%) and OS (91% vs 52%) [18]. In our analysis patients with lymph node metastases had worse five-year survival rates for all endpoints and respectively for LRC (94.5% vs 77.1%, $p < 0.001$), for DFS (65.6 % vs 88.5%, $p < 0.001$), for DSS (78.1% vs 94.9%, $p < 0.001$); and for OS (71.2% vs 89.1%, $p < 0.001$).

Recently metastatic lymph node ratio has been introduced in surgical oncology as a prognostic factor for several cancer types such as colorectal cancer and pancreatic cancer [19, 20]. Researchers from Vienna evaluated the impact of lymph node density (LND) (the ratio of positive lymph nodes to the total number of lymph nodes removed) on survival in 88 cervical cancer patients treated with postoperative radiochemotherapy. They stratified patients into two groups according to LND; patients with LND ≤ 10% versus patients with LND > 10% and demonstrated that patients with LND > 10% had impaired DFS and OS rates compared with patients with LND ≤ 10% [21]. We demonstrated that patients with MLNR > 10% had poorer survival rates for all endpoints of the study (LRC, DSS, DFS and OS). Five-year overall survival rate was 63% for the patients with MLNR > 10% and 80% for the patients with MLNR ≤ 10%.

During the pelvic lymph node dissection for cervical cancer it is suggested to dissect as many of the nodes as possible. The average number of lymph nodes need to be removed is 25-35 [22]. It is well documented that the percentage of nodal involvement increases from 10.5% positive nodes when less than 20 nodes are removed; to 26.5% when more than 50 nodes are removed [23]. Pieterse *et al*. conducted a prospective trial and demonstrated that the extent of lymphadenectomy significantly affected DFS in patients with pelvic LNs metastases. In

patients with less than ten LN dissected in that particular study, 5-year DFS was less than 20% [24]. In our series the median and the mean number of removed lymph nodes were 20 and 23, respectively (range: 1-95). We observed slightly lower LRC, DFS, DSS and OS rates for patients with ≤ 20 LNs dissected but the differences were not statistically significant. It is possibly due to the administration of postoperative pelvic RT which controls possible subclinical disease in the non dissected pelvic lymph nodes.

There are several unfavorable prognostic factors that researchers reached consensus; these are advanced stage, large tumor volume (> 4 cm), deep stromal invasion, lymphovascular invasion, as well as parametrial involvement and close/positive surgical margins in patients with early-stage cervical cancer [18]. In these cases, most studies indicate that adjuvant radiation therapy could improve prognosis even if lymph nodes are negative [3, 24]. Atahan *et al*. reported the treatment results of 141 patients treated with surgery and postoperative RT/RCT and multivariate analysis revealed that the level and the number of metastatic lymph nodes and administration of concomitant chemotherapy were prognostic factors for OS, DFS and LRFS. Moreover endometrial involvement was found significant for DFS and distant metastases free survival (DMFS) [9]. In the current analysis we demonstrated poorer OS rate for advanced stage, poorer LRC rate for the presence of LVSI, and poorer LRC, DFS, DSS and OS rates for bulky tumor (> 4 cm), poorer DFS, DSS and OS rates for parametrial invasion, poorer LRC, DFS and DSS rates for endometrial involvement and poorer DSS for positive surgical margin.

The influence of age and histopathologic type on LRC and survival is not clearly determined and the results of previous studies have been inconclusive [2]. In our analysis patients younger than 47 years of age had better OS rates. We did not observe any LRC control or survival difference among histopathological types.

The impact of treatment break on local control and survival has already been shown in RT/RCT trials for curatively treated head and neck and cervix cancer patients. For cervical cancer, prolongation of the overall treatment time is associated with an estimated loss of local control of 0.3-1.6% daily [2]. In our analysis treatment break > 14 days is associated with decreased DFS and DSS rates.

Tumor hypoxia has been linked to tumor progression, the development of treatment resistance, and thus poor prognosis [2]. It has been known that Hb level has an impact on tumor oxygenation and low Hb levels decrease the radioresponsiveness of the tumor. Mayr *et al*. analyzed 88 cervical cancer patients treated with RCT and demonstrated that low Hb (< 11.2 g/dl) level is associated with lower LRC and DSS rates [25]. In the current analysis patients with Hb level ≤ 10 g/dl had statistically significant poorer OS rates (66.7% vs 97%) compared to patients with > 10 g/dl.

The locoregional and survival rates of patients with parametrial invasion and positive surgical margin were found to be poorer even with the administration of RT/RCT. Therefore during the preoperative gynecologic examination the gynecologist should discriminate patients who may need postoperative RT and refer these patients to a radiation oncologist. Moreover selecting single modality treatment will protect the patient from increased side-effects of mutimodality treatment [1].

In the literature, the rate of late toxicities range from 3% to 30%. This wide range is due to the differences in reporting (all grades vs grade 3-4) and utilization of various toxicity systems (RTOG vs LENT-SOMA). Among these studies gastrointestinal toxicity appears to be the most common toxicity followed by genitourinary toxicity. The GOG 92 trial reported 6.6% grade 3-4 toxicity in the RT arm and 2.1% toxicity in the observation arm [3]. Recent studies reported grade 3-4 late toxicities between 3%-4.7% [2]. Atahan *et al*. reported the rate of all grade 3-4 late toxicity in eight (6%) patients including both gastro-intestinal (GI), and genito-urinary (GU) toxicity [9]. During a median of 60.5 months (range: 6-202 months) of follow-up, grade 3-4 late GI toxicity in eight (3.2%) and GU in four (1.6%) and skin toxicity in two (0.8%) were observed in our series. The incidence of grade 3 and 4 late toxicities seen in our study was similar to the other mentioned series [3, 9].

In conclusion, our analysis yields similar results with the published literature on the treatment outcome of early-stage cervical cancer. External RT combined with brachytherapy provides satisfactory local control and survival rates. Lymph node metastases, higher MLNR, tumor size (> 4 cm), endometrial involvement, and low Hb status seem to be the most important prognostic factors for early-stage cervical cancer.

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