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Treatment of Invasive Cervical Cancer: Rijeka Experience

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A B S T R A C T

The aim of this retrospective analysis was to evaluate the survival rate in 661 patients with cervical cancer regarding two time periods 1990–1996 and 1997–2003 and the specific stage related risk factors. The respective five-year survival was 71.7% and 80.0%. Analyzing the risk factors in the univariate and multivariate regression modalities ultimately only two parameters, the two time periods and FIGO staging were found to be independent prognostic factors. The observed total improvement in the survival rate of the second time period is followed by an increase in conservative surgery in stage T1A1, a reduction in the use of adjuvant radiotherapy among operable stages T1b1, T1b2 and T2A, while the treatment of locally advanced cervical cancer did not differ significantly.

Key words: *cervical cancer, treatment, staging, FIGO, TNM, survival*

Introduction

Cervical cancer is the second most common malignancy in women worldwide. Although it has been considered a preventable cancer because of cervical cytological screening programs and effective treatment of preinvasive lesions, the mortality rate is still high.

In Croatia during last decade the incidence of cervical cancer was about 16 patients per 100,000 women a year, reaching an incidence of 13.7 patients per 100,000 women in 2003[1].

Risk factors in developing cervical cancer include young age at first intercourse, multiple sexual partners, cigarette smoking, high parity and low socioeconomic status. There is some relationship to oral contraceptives as risk factors in cervical cancer development with a possible small increase[2]. However, infection with the human papillomavirus (HPV) has been detected in up to 99% of women with squamous cervical cancer and is defined as the principal risk factor in cervical cancer development[3].

Until recently, major breakthroughs in reducing the incidence and mortality of cervical cancer have occurred because of the widely used screening programs. The Papanicolaou test, known as the Pap test, has been the most cost- effective cancer-screening test ever developed. In Rijeka, Croatia, the Pap-test was introduced as a routine test in gynecologic examination since 1960[4].

Nevertheless, cervical cancer is still present in our population and affected patients require diagnosing and treatment that consists of four steps: establishing the diagnosis, defining the extent of the disease, determining and conducting the optimal treatment and follow-up of patients for evidence of recurrence and/or treatment related complications.

The diagnosis of cervical cancer is made exclusively by histological analysis of a biopsy specimen or by conization. Once histological diagnosis is arrived at, based on the International Federation of Gynecology and Obstetrics (FIGO) classification, clinical (preoperative) staging has to be defined. Conization may be part of diagnostic workup, however, its role in definitive treatment will be discussed later. Diagnostic workup is necessary to de-

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fine preoperative staging using only: physical examination, colposcopy, cervical or cone biopsy, cystoscopy, lower gastrointestinal endoscopy or barium enema, intravenous pyelography and chest radiography. Computed tomography (CT) and magnetic resonance (MRI) and positron emission tomography with computerized tomography (PET-CT scan) are very useful tools for better definition of the disease presence, but FIGO is not taken into account as a staging modality. The treatment strategies for cervical cancer are related to the diagnosis and the clinical staging system.

The aim of this retrospective analysis was to evaluate the survival rate regarding two time periods 1990–1996 and 1997–2003 and the specific stage related risk factors.

Subjects and Methods

Medical records of all patients with cervical cancer primarily treated at the Clinical Hospital Center Rijeka between 1990 and 2003 were retrospectively reviewed. The hospital is a tertiary referral center and educational base of the University of Rijeka, School of Medicine for the surrounding area of three counties including about 550,000 inhabitants. Six hundred and sixty one patients with primary cervical cancer were identified.

The prognostic variables investigated for this study included two time periods, the first from 1990 to 1996, and the second from 1997 to 2003. December 31, 2006 was the cut off date for patient follow-up

In both time periods we analyzed the following prognostic variables: T stage[5], FIGO stage according to the last revision of cervical cancer staging[6] and compared the 5-year survival rate between each subgroup of patients and the entire group. The stage indicated in this study referred to pathologic examination after primary surgery and clinically in cases where radiotherapy or chemo-irradiation was the first therapeutic option. During the observed period, cervical cancer treatment was based on guidelines agreed at the national and hospital level. The surgical approach was primarily applied to clinical FIGO stages IA1 to IIA. In stage IIB the primary treatment approach depended on the clinician. In higher stages radiotherapy was the treatment of choice. The guidelines on adjuvant radiotherapy after surgery changed during the two time periods as well as those on the conservative option in the treatment of the early stage.

The groups of patient with histology defined as FIGO Ia1 stage (stromal invasion of not >3.0 mm in depth and extension of not >7.0 mm) were analyzed separately to compare the type of treatment and the 5-year survival rate between the two time periods. Stage IA1 and stage IA2 cervical cancer were diagnosed either on cone or hysterectomy (simple or radical) specimen.

All cone biopsies were bisected and each half was embedded completely and serially processed into 40–90 individual sections. The cervices of the extirpated uteri were treated as a cone and sampled by conventional methods. Groups of patients with stage disease of IB1 and higher underwent clinical and instrumental staging. In particular, stage T1b1, T1b2 and T2a tumor size was assessed by pelvic examination and under anesthesia at the time of biopsy or surgery. The definitive tumor dimension in patients undergoing surgery was determined by measuring the tumor after uterus removal, while in patients without surgery the definitive dimension was determined clinically. All patients treated before the last revision of FIGO staging in 1994 were restaged according to the new recommendations[6].

In the group of patients with pathologic T stages T1b1, T1b2 and T2a the following categorical variables were evaluated and compared in the two time periods (1990–1996 vs. 1997 to 2003): the tumor diameter (less than 2 cm, 2 to 4 cm, more than 4 cm), age (under 40, 40 to 59, 60 years and over), histology (squamous and adenocarcinoma), tumor differentiation (G1 – well, G2 – moderate and G3 – poor), T stage, FIGO stage, lymph node involvement (Nx – not assessed, No – negative node, N1 – positive node), lymphovascular space involvement (No – Yes) and the mode of treatment (assigned in each table).

Statistics

Absolute numbers with percentages were used to show the number of patients per group. The Chi-square test was used where appropriate. The Kaplan-Meier method was used to estimate the survival curves. Survival time was calculated in months from the date of surgery or therapy beginning at either the date of death, or the date of last follow-up visit for surviving patients. Univariate analysis of categorical variables was performed for prognostic significance using the Cox proportional hazard model and the log-rank test for significance, respectively. Variables with $p<0.10$ on univariate analysis were then included in a multivariate Cox proportional hazard regression analysis. Statistical analyses were performed using MedCalc for Windows, version 9.2.0.2 (MedCalc Software, Mariakerke, Belgium).

Results

The distribution of »T stage« among cervical cancer patients in the two time periods, the survival in each stage and the survival per entire group are presented (Table 1). Staging is the most important predictor of survival, reflecting the extent of the disease with the risk of death being higher as a stage increases. Comparing total survival between the two periods, there is a clear statistically significant higher 5-year survival rate among patients treated in the second time period. The group of patients in T1B1 stage treated in the second period had a significantly better survival rate than the same staged patients treated in the first period. However, there was no difference in patient distribution per stage (Chi-square=0.9, p=0.34; not shown). The evaluated patient age is equal in both time periods (48.7 vs. 48.6 years).

TABLE 1
DISTRIBUTION AND SURVIVAL OF CERVICAL CANCER PATIENTS (n=661) ACCORDING TO THE »T« STAGE AND TIME PERIOD

Stage	Period 1990–1996				Period 1997–2003				Statistical significance for survival
	n	(%)	–	5-years survival	n	(%)	–	5-years survival	
T1A1	115	(37.6)	–	100%	145	(40.8)	–	98.4%	NS
T1A2	9	(2.9)	–	100%	5	(1.4)	–	100%	NS
T1B1	69	(22.5)	–	80.2%	85	(23.9)	–	94.2%	p=0.017
T1B2	14	(4.6)	–	60.9%	25	(7.0)	–	77.6%	NS
T2A	8	(2.6)	–	50.0%	6	(1.7)	–	100%	NS
T2B	43	(14.1)	–	40.8%	26	(7.3)	–	53.4%	NS
T3A	2	(0.7)	–	0.0%	2	(0.6)	–	0.0%	NS
T3B	43	(14.1)	–	21.3%	56	(15.8)	–	23.2%	NS
T4	3	(1.0)	–	0.0%	5	(1.4)	–	0.0%	NS
Total	306		–	71.7%	355		–	80.0%	p=0.02

Distribution of patients in the FIGO stage shows no difference (Chi-square=14.8, p=0.098; not shown) between the two time periods (Table 2). The 5-year survival rate in stages IA1 and IA2 is excellent in both time periods. Stages IB1, IB2, IIA, IIB and IIIB in the second time period had better survival rates but without statistical significance. Nevertheless, a total 5-year survival rate is significantly higher in the second time period (Table 2).

In our study, FIGO stage IA1 was present in 260 (39.3%) out of 661 patients (Table 3). In the second time period we found an increase from 37.6% to 40.8% without statistical significance (Chi-square=0.60, p=0.4; not shown) of patients with stage IA1 (Table 2). The types of patient treatment in stage IA1 are presented in the Table 3. The distribution of patients regarding the mode of

TABLE 3
TREATMENT OF CERVICAL CANCER PATIENTS IN T STAGE T1A1 (n=260)

Mode of treatment	Period 1990–1996 n=115		Period 1997–2003 n=145	
	n	(%)	n	(%)
Conisation	54	(47.0%)	84	(58.0%)
Hysterectomy	35	(30.4%)	35	(24.1%)
Hysterectomy & Lymphadenectomy	23	(20.0%)	16	(11.0%)
Radical hysterectomy & Lymphadenectomy	*3	(2.6%)	10	(6.9%)

*2 patients treated with adjuvant radiotherapy

TABLE 2
DISTRIBUTION AND SURVIVAL OF CERVICAL CANCER PATIENTS (n=661) ACCORDING TO THE FIGO STAGE AND TIME PERIOD

Stage	Period 1990–1996				Period 1997–2003				Statistical significance for survival
	n	(%)	–	5-years survival	n	(%)	–	5-years survival	
IA1	115	(37.6)	–	100%	145	(40.8)	–	98.4%	NS
IA2	9	(2.9)	–	100%	5	(1.4)	–	100%	NS
IB1	59	(19.3)	–	87.5%	76	(21.4)	–	93.5%	NS
IB2	13	(4.2)	–	66.1%	18	(5.1)	–	81.6%	NS
IIA	7	(2.3)	–	57.1%	6	(1.7)	–	100%	NS
IIB	36	(11.8)	–	43.2%	18	(5.1)	–	61.4%	NS
IIIA	2	(0.7)	–	0.0%	2	(0.6)	–	0.0%	NS
IIIB	61	(19.9)	–	24.8%	74	(20.8)	–	40.8%	NS
IVA	2	(0.7)	–	0.0%	4	(1.1)	–	0.0%	NS
IVB	2	(0.7)	–	0.0%	7	(2.0)	–	0.0%	NS
Total	306		–	71.7%	355	–	80.0%	p=0.02	

treatment and the time periods shows high significance (Chi-square=13.87, p=0.008). An increase in conservative surgical treatment requiring only conization is identified in 58% of cases in the second time period, while hysterectomy decreased from 30.4% to 24.1%, also in the second period. Radical procedures, including lymph node assessment, mainly due to lymph-vascular space involvement, were present in a similar percent in both observed periods. The apparent increase in the use of radical hysterectomies in the second time period is due to dubious biopsy material in some patients. However, in the second time period lymph node staging and/or radical hysterectomy dropped from 22.6% to 17.9% (not shown). During the first time period two patients received adjuvant pelvic irradiation.

»T« stage was used to evaluate the dimension of primary tumor in women with cervical cancer localized in the cervix (stage T1b1 and T1b2) and with only vaginal involvement (T2a), excluding parametrial involvement. In this group all patients with a concomitant serious medical condition were not treated or were treated with palliative radiotherapy. In the medically uncompromised patients older than 75 years primary treatment included primary radiotherapy. Patients with primary surgery were divided into two groups with respect to the use of adjuvant pelvic irradiation. The indications for adjuvant pelvic irradiation were changed during the observed time. The first group of patients consisted of those with stage from T1B1 to T2A and a dimension of cervical cancer less than 2 cm in diameter. The next group of patients included tumor diameters of 2 to 4 cm and the third group of patients included tumors of a diameter larger than 4 cm. Patients staged T2b and T3b were not divided in the subgroups. Results are presented as a total number of patients while percents include the proportion of the entire group within the stage categories (Table 4).

In the group of patients with the tumor diameter less than 2 cm we observed an obvious inversion in the use of

TABLE 4
TREATMENT OF CERVICAL CANCER PATIENTS REGARDING T STAGE AND TUMOR DIMENSION

T stage & tumor dimension	Type of treatment	Period 1990–1996		Period 1997–2003	
		n	(%)	n	(%)
T1b1-T2a (< 2cm)	Without therapy	0		0	
	Radiotherapy	2	(7.4%)	1	(2.1%)
	Radical surgery	7	(25.9%)	36	(75.0%)
	Radical surgery & adjuvant radiotherapy	18	(66.7%)	11	(22.9%)
	Overall survival	96.3%		96.7%	
T1b1-T2a (2–4 cm)	Without therapy	0		1	(2.4%)
	Radiotherapy	2	(4.4%)	1	(2.4%)
	Radical surgery	2	(4.4%)	18	(43.9%)
	Radical surgery & adjuvant radiotherapy	41	(91.2%)	21	(51.3%)
	Overall survival	69.3%		87.1%	
T1b2-T2a (>4 cm)	Without therapy	1	(5.3%)	0	
	Radiotherapy	2	(10.5%)	3	(11.1%)
	Radical surgery	0		7	(25.9%)
	Radical surgery & adjuvant radiotherapy	16	(84.2%)	17	(63.0%)
	Overall survival	54.9%		87.7%	
T2b	Without therapy	2	(4.7%)	0	
	Radiotherapy	27	(62.8%)	12	(46.2%)
	Radical surgery	1	(2.3%)	0	
	Radical surgery & adjuvant radiotherapy	13		14	(53.8%)
	Overall survival	40.8%	(30.2%)	53.4%	
T3b	Without therapy	6	(14.0%)	10	(17.9%)
	Radiotherapy	37	(86.0%)	44	(78.6%)
	Radical surgery	0		0	
	Radical surgery & adjuvant radiotherapy	0		2	(3.5%)
	Overall survival	21.3%		23.2%	

adjuvant pelvic irradiation in the second time period (Chi-square=17.04, p=0.0002; not shown) with a similar five-year survival rate. In these groups of patients only one patient with positive pelvic lymph node was identified in the second time period.

In the group of patients with primary cervical tumor diameter of 2 to 4 cm an inversion of treatment modalities was identified (Table 4). Namely, the majority of cervical cancer patients in the first time period were treated with adjuvant pelvic irradiation with a 5-year survival rate of 69.3%. In the second time period there was a significant difference in patients distribution (Chi-square =20.44, p= 0.0001; not shown), with a decrease in the use of adjuvant pelvic irradiation after radical surgery and a total increase of the 5-year survival rate. In the first time period 10 (23.2%) patients had positive lymph nodes, while in the second time period positive nodes were found in 8 patients (20.5%).

In the group of patients with primary cervical tumor greater than 4 cm primary radiotherapy was applied in about 11% (Table 4). All patients who underwent surgery in the first time period were adjunctively treated with pelvic irradiation. In the second time period one fourth of patients were treated only with radical surgery. Although there is no significant change in the modality of treatment in the second time period, the 5-year survival rate is significantly higher (Chi-square=6.05, p=0.014; not shown). However, in the second time period a trend of decrease in the use of adjuvant radiotherapy was also observed. Analyzing the rate of positive lymph nodes we identified 10 out of 16 patients (62.5%) in the first time group and 8 out of 24 (33.3%) patients in second time period. The observed difference had no statistical significance (Chi-square=2.26, p=0.135; not shown).

In patients with T2B stage in the first time period the therapy mostly used was radiotherapy (Table 4). In the second time period radical surgery with adjuvant pelvic irradiation was encountered in a higher proportion. The difference of the treatment modality distribution is not significant. The 5-year survival rate, although higher in the second time period, did not reach a statistical significance.

Clinically staged patients in stage T3B in both time periods received similar treatment options (Table 4). The majority of patients were treated with primary radiotherapy, while only a small number of patients after the year 2001 received combined chemoirradiation. The rate of survival in both time period groups was similar.

The patient groups staged T1B1 to T2B and T3B with 177 and 198 patients had a 5-years survival rate of 54.6% and 68.1% in first and second time period, respectively (Logrank test p=0.0124; not shown).

Univariate analysis of variables was performed in the entire group of cervical cancer patients (n= 661). Variables, two time periods, histology, FIGO stage, degree of differentiation (G), T stage, lymph node status, type of treatment and patient age were categorized as shown (Table 5). All analyzed variables were significant, and were subsequently included in the multivariate model. Using Cox proportional hazard regression only two variables remained significant: two time periods and FIGO stage (Table 6).

Discussion

The distribution of cervical cancer patients regarding T stage and FIGO stage are similar during the two observed periods. Approximately 40% of patients with cervical cancer presented with a microinvasive disease limited to the invasion of 3 mm and 7 mm or less in width. The diagnosis of stage IA1 cervical cancer has to be established at least via cone specimen. Acceptable methods for diagnostic purposes are cold knife conization and loop electrosurgical excision. The prognosis is excellent, as shown in our series. A total 5-year survival for 260 patients presented with microinvasive cervical cancer in our analysis is 99.1% (not shown). There is no difference in the 5-year survival between the two time period groups. In the last FIGO analysis 829 (7.12%) patients with cervical cancer stage IA1 out of 11639 had a five-year survival rate of 97.5%[7]. There are a significantly smaller proportion of patients with microinvasive cervical cancer in world statistics compared to our patients (7.12% vs 39.3%). A relative increase in the total number as well as in the proportion of the entire cervical cancer group could be attributed firstly to the meticulous analysis of cervices with multiple serial sections per specimen.

Surgical treatment of patients with cervical cancer stage IA1 moved to conservative treatment is present in almost 60%. Hysterectomy is reserved primarily for women that are past childbearing. Lymphadenectomy is reserved for those with lymph space involvement, although there is little, if any risk of lymph node metastasis, recurrence and death[8–10]. Of the 52 patients (not shown) in our series treated with lymphadenectomy as part of treatment option firstly due to lymph vascular space involvement, none had lymph node metastasis.

The 5-year survival rate in our group of patients is rather high but without statistical significance (99.1% vs 97.5%). In one series with median follow-up of 45 months, 10% of patients developed cervical intraepithelial neoplasia 3 – CIN III[11]. In our series of 126 patients with cervical cancer stage IA1 treated with a conservative surgical procedure the cold knife conization and a median follow-up of 72 months, we detected local recurrence in form of cervical intraepithelial neoplasia irrespective of their severity in 7 (4%) patients (data not shown).

Squamous lesions are predominantly present in the early stage of cervical cancer stage IA1, while glandular lesions are rarely recognized in the early stage. This is mainly due to difficulties in measuring the glandular lesions invasion depth. In our series of 260 patients with cervical cancer stage IA1 we identified 6 (2.3%) patients with glandular lesions (data not shown). Currently, the options of treatment modalities based on retrospective data include the same procedures with the same indications as a squamous lesion[12,13].

TABLE 5
UNIVARIATE ANALYSIS OF CERVICAL CANCER PATIENTS (n=661)

Parameter		Number of patients	5-year survival	Chi-square	Significance level	Hazard ratio	(95% CI)
Period	1990–1996	(306)	72.0%	Reference			
	1997–2003	(355)	80.0%	5.4	p=0.02	1.46	(1.06–2.02)
Histology	Squamous	(583)	77.3%	Reference			
	Adeno	(78)	65.5%	7.2	p=0.0074	0.57	(0.29–0.83)
FIGO	IA1	(260)	99.1%	Reference			
	IA2	(14)	100.0%	0.1	p=0.74	1.01	(0.01–1571)
	IB1	(135)	91.0%	17.0	p<0.0001	0.08	(0.03–0.29)
	IB2	(31)	74.4%	50.8	p<0.0001	0.03	(0.00–0.003)
	IIA	(13)	76.9%	38.1	p<0.0001	0.03	(0.00–0.0001)
	IIB	(54)	46.8%	161.0	p<0.0001	0.01	(0.00–0.003)
	IIIA	(4)	0.0%	315.0	p<0.0001	0.004	(0.00–0.00001)
	IIIB	(135)	33.3%	243.0	p<0.0001	0.008	(0.01–0.03)
	IVA	(6)	0.0%	271.9	p<0.0001	0.005	(0.0000–0.0000)
	IVB	(9)	0.0%	337.7	p<0.0001	0.005	(0.0000–0.0000)
Gradus	G1	(42)	87.5%	Reference			
	G2	(260)	57.8%	10.9	p=0.001	0.25	(0.25–0.70)
	G3	(104)	59.5%	9.6	p=0.002	0.26	(0.20–0.69)
	Undetermined	(255)	99.1%	20.8	p<0.0001	0.06	(0.00–0.05)
T-stage	T1A1	(260)	99.1%	Reference			
	T1A2	(14)	100.0%	0.1	p=0.74	–	
	T1B1	(154)	88.1%	24.8	p<0.0001	0.06	(0.04–0.25)
	T1B2	(39)	70.5%	64.9	p<0.0001	0.03	(0.0001–0.004)
	T2A	(14)	70.7%	54.6	p<0.0001	0.02	(0.0000–0.0000)
	T2B	(69)	45.2%	180.5	p<0.0001	0.01	(0.001–0.007)
	T3A	(4)	0.0%	315.9	p<0.0001	0.004	(0.0000–0.0000)
	T3B	(99)	21.7%	307.5	p<0.0001	0.007	(0.002–0.007)
	T4	(8)	0.0%	327.6	p<0.0001	0.005	(0.0000–0.0000)
Lymph	Nx	(389)	69.9%	Reference			
node	No	(224)	92.3%	40.2	p<0.0001	4.6	(2.22–4.52)
status	N1	(48)	49.0%	7.0	p=0.008	0.55	(0.27–0.82)
Therapy							
Wertheim (W)	(85)	94.5%	Reference				
Without therapy	(21)	0.0%	138.0	p<0.0001	41.5	(1416–25897)	
Radiotherapy	(138)	33.8%	74.0	p<0.0001	20.6	(4.19–9.77)	
Conisation	(138)	98.4%	2.2	p=0.1	0.3	(0.05–1.5)	
Hysterectomy	(71)	100.0%	3.5	p=0.06	0.0	(0.02–1.1)	
Hysterect. & adj. radiotherapy (7)	68.6%	7.5	p=0.006	7.5	(3.7–2707)		
Hysterect. & lymhadenect.	(40)	100.0%	2.0	p=0.16	0.0	(0.03–1.79)	
Hysterect. & lymhadenect. & adjuvant radiotherapy	(13)	44.0%	34.6	p<0.0001	15.4	(50.8–2573)	
Wertheim & adj. radiotherapy	(148)	77.3%	11.7	p=0.0006	0.2	(0.16–0.61)	
Age	< 40	(229)	93.8%	Reference			
(years)	40–59	(260)	79.2%	21.6	p<0.0001	0.26	(0.19–0.51)
	≥ 60	(172)	48.1%	111.2	p<0.0001	0.09	(0.07–0.18)

TABLE 6
COX PROPORTIONAL HAZARDS REGRESSION OF CERVICAL CANCER PATIENTS (n=661)

Parameter	Significance level	Hazard ratio	(95% CI)
Period (1990–1996 and 1997–2003)	p=0.012	0.66	(0.48–0.91)
Histology	p=0.08 (NS)	1.47	(0.96–2.25)
FIGO	p=0.0001	1.5	(1.23–1.83)
Tumor differentiation (G)	p=0.21 (NS)	1.2	(0.91–1.57)
Lymph node status	p=0.47 (NS)	0.8	(0.41–1.50)
T stage	p=0.16 (NS)	1.16	(0.94–1.41)
Therapy	p=0.92 (NS)	0.99	(0.85–1.15)
Patients age	p=0.47 (NS)	1.11	(0.84–1.46)

Categories of variables as shown in Table 5, NS – non-significant

The patients with cervical cancer stage IA2 are present in a small percentage (2.9%). The rate (2.4%) of this stage is similar to that in the last FIGO statistics[7]. The diagnosis of stage IA2 cervical cancer should also be established via cone biopsy. Although the prognosis for these patients is also excellent (in our statistics 14 patients had a 5-year survival rate of 100%, while in previously mentioned statistics the survival rate in 275 patients was 94.8%) they are at higher risk for lymph node metastasis and treatment failure. In one series a 6.8% incidence of lymph node metastasis in patients with cervical cancer stage IA2 is reported[10]. Currently, there is a shortage of plausible recommendations for the management of cervical cancer in stage IA2 based on reliable and prospective studies. Until more data become available pelvic lymph node assessment is necessary. Hysterectomy could be performed as a simple procedure, while radical hysterectomy represents surgical trauma without confirmed survival advantage. In patients with desired childbearing, large conization with absolute clear margins and negative lymph node could be the treatment of choice[14].

The treatment of choice in cervical cancer stages IB1 to IIA can be influenced by patient age, coexisting medical conditions and physician bias. Retrospective as well as prospective studies comparing radical surgery with pelvic radiation therapy showed similar survival rates[15,16]. Radical surgery offers few advantages in respect to preservation of ovaries with fewer detrimental effects on vaginal function. The advantages of radical surgery over radiotherapy can be eliminated in patients receiving postoperative adjuvant radiotherapy. Indication for the use of adjuvant radiotherapy includes positive lymph node, positive margins and parametrial involvement. Other indications for the use of postoperative radiotherapy in cases without evidence of disease outside the cervix include the presence of high risk factors in the hysterectomy specimen like large tumor diameter, deep cervical stromal invasion and the invasion of lymph vascular space involvement[17]. As tumor diameter increases, the risk of treatment failure is greater. Tumor diameter greater than 4 cm leads to the use of various treatment regimens. The T stage T1B2 includes radical hysterectomy with pelvic and paraaortic lymphadenectomy followed by tailored chemoradiation therapy for high-risk patients, radiation therapy followed by extrafascial hysterectomy, radiation therapy plus concurrent chemotherapy and neoadjuvant chemotherapy followed by radical pelvic surgery[18,19]. Although some authors recommend the use of concurrent radiotherapy and chemotherapy as an optimal treatment option[19], radical hysterectomy with tailored chemoirradiation for high-risk patients is the most cost-effective strategy to manage Stage IB2 cervical cancer, resulting in a 5-year survival of approximately 70%. In our series we present only 3 patients treated with primary radiotherapy, 7 treated with radical hysterectomy and 17 patients treated with radical hysterectomy and adjuvant radiotherapy with a total 5-year survival of 87.7%. Radical surgery followed by tailored radiotherapy is especially suitable in settings where resources are limited. Adding radiotherapy and chemotherapy in form of neoadjuvant chemotherapy unnecessarily increases the total cost without clear advantage in a 5-year survival[18].

Comparing the use of adjuvant radiotherapy between the two time periods in our series we found that in cases with a tumor diameter less than 2 cm reduction in the use of radiotherapy did not influence the 5-year survival rate. In the group of patients with cervical cancer of diameters from 2 to 4 cm the observed reduction in the use of adjuvant radiotherapy lead to a better 5-year survival. In the group of patients with cervical cancer stage IB2 (tumor diameter greater than 4 cm) adjuvant radiotherapy in the second time period was in part reduced with a higher 5-year survival.

From our results, the philosophy of treatment in the second time period is one of the significant points in the treatment acceptance and success measured through a 5-year survival. The lack of this analysis precludes the precise definition of all elements used in building the indications for adjuvant radiotherapy during the observed period. Moreover, the indications for adjuvant radiotherapy after radical surgery changed several times, especially in the second time period. Conclusively, from the retrospective results and the results of others[20,21] adjuvant radiotherapy seems to be useful only in the group of patients with the disease beyond the cervix, i.e., lymph node metastasis and parametrial involvement.

The standard accepted therapy in the last 15 years for locally advanced cervical cancer includes radiotherapy present in the majority of cases in our series. The addition of cisplatin or a cisplatin containing regimen to a radiation therapy results in better disease control and a 5-year survival[22,23]. It is part of a standard recommended therapy. A subsequent meta-analysis of 19 randomized controlled trials including 4560 patients confirmed the effectiveness of concurrent chemotherapy and radiation therapy, which improved the overall survival of patients with a locally advanced disease[24]. The new therapeutic option in patients with locally advanced cervical cancer promoted by Croatian authors[25] seems to produce higher survival rates, but the preliminary results have to be confirmed in large multicenter trials.

In our series of patients in stage T2B or greater even though the 5-year survival rate is better, the difference has not reached statistical significance. In stage T2B a more extensive use of radical surgery with adjuvant radiotherapy and better survival had also no statistical significance. A minor number of patients in stage T3B were treated with the use of chemoirradiation, which was not taken into account in the actual analysis, and we have not performed statistical evaluation regarding the application of concurrent chemotherapy and radiation therapy in patients with locally advanced cervical cancer.

Conclusions

The comparison of two time periods, 1990–1996 and 1997–2003, showed an overall higher five-year survival rate in the second time period denoting a significant independent prognostic parameter. The observed total improvement in survival rates was followed by an increase in conservative surgery in stage T1A1, reducing the application of adjuvant radiotherapy in operable stages T1B1, T1B2 and T2A, while the treatment of locally advanced cervical cancer has not differed significantly.

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LIJEČENJE INVAZIVNOG RAKA VRATA MATERNICE: ISKUSTVO RIJEKE

SAŽETAK

Cilj ovoga retrospektivnog rada uključuje analizu preživljavanja u 661 bolesnice s rakom vrata maternice obzirom na dva razdoblja, 1990–1996 i 1997–2003 kao i specifičnih čimbenika rizika obzirom na stadije bolesti. Petogodišnje preživljavanje prve skupine iznosilo je 71,7%, dok je u drugoj skupini ono iznosilo 80,0%. Analizirajući čimbenike rizika u univarijatnoj, te u multivarijatnom regresijskom modelu naposljetku samo dva parametra, vremenska razdoblja i FIGO stadij imaju nezavisni prognostički značaj. Opaženo bolje preživljavanje u drugom vremenskom razdoblju praćeno je povećanjem konzervativnih operativnih zahvata u FIGO stadiju IA1, smanjenjem primjene adjuvantne radioterapije među bolesnicama operabilnog stadija T1b1m T1b2 i T2A, dok se liječenje lokalno uznapredovanog raka vrata maternice nije bitno razlikovalo obzirom na vremenska razdoblja.