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RESEARCH

Pathologic Complete Remission after Preoperative High-Dose-Rate Brachytherapy in Patients with Operable Cervical Cancer: Preliminary Results of a Prospective Randomized Multicenter Study

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Abstract The role of preoperative intrauterine brachytherapy (BT) in the multidisciplinary treatment of early stage cervical carcinoma (ESCC) is controversial. In 2005, a prospective randomized multicenter study was initiated in Hungary in order to explore the potential advantages of preoperative high-dose-rate (HDR) BT. In this article we evaluate the efficiency of preoperative HDR BT by the rate of pathologic complete remission (pCR) in the first 185 patients enrolled in the study at the National Institute of Oncology and at the Uzsoki Municipal Cancer Center in collaboration with the 1st Department of Gynaecology and Obstetrics of Semmelweis University, Budapest, Hungary. In arm A, patients received 2x8Gy preoperative intracavitary HDR BT, while in arm B no preoperative treatment was given. In both arms patients underwent radical Wertheim (Piver III) hysterectomy. The pCR rate was 25.7% after preoperative HDR BT, while it was only 11.2% with surgery alone (p=0.03), in these cases the tumor was eliminated during the diagnostic excision or conisation. The rate of positive surgical margins was 1.5% after preoperative BT, while it was as high as 11.4% without preoperative RT (p=0.02). There was no significant difference in the local tumor control (LTC), distant metastases free survival (DMFS) and overall survival (OS) between the two arms. According to our preliminary results preoperative intracavitary HDR BT significantly increases the rate of pCR and decreases the rate of positive surgical margins in patients with ESCC. Longer follow-up is required to establish the possible impact of pCR on the ultimate LTC and OS.

Keywords Cervical cancer · Preoperative brachytherapy · Pathologic complete remission · Surgical margins

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Introduction

Several treatment options are available for the management of early stage cervical cancer (ESCC), including surgery alone, preoperative radiotherapy (RT) followed by laparotomic or laparoscopic surgery, primary surgery followed by

postoperative RT or radio-chemotherapy (RChT), neoadjuvant chemotherapy (ChT) and surgery, RT alone, and concomitant RChT [1–3]. The optimal treatment algorithm should be chosen individually for each patient by a multidisciplinary team, based on international and national guidelines, taking into consideration the stage, histology, and patient's status.

It is widely accepted that in situ (stage 0) and stage IA1 carcinomas can be treated by surgery alone (conization, trachelectomy or hysterectomy). If surgery is contraindicated, intracavitary brachytherapy (BT) alone can be performed. Guidelines unanimously recommend RChT in advanced stages: II/B distal, III/A-B and IV/A, while in stage IV/B palliative treatment (ChT or RT) is recommended. However, there is no general consensus regarding the optimal treatment of stage IA2, IB1, IB2, IIA1, IIA2, and proximal IIB diseases. Certain institutions, mainly in France and Sweden, perform RT before the surgical intervention, while in Anglo-Saxon countries primary surgery is preferred, followed by postoperative RT, or RChT in selected patients [3–9].

Many decades of experience with preoperative RT have been accumulated in Hungary [10–14]. However, in the absence of prospective randomized studies, there is no level I-II evidence regarding the advantages or eventual disadvantages of preoperative BT. Several retrospective single-institution single-arm studies (evidence level III-IV) evaluate the outcomes of surgery alone or BT followed by surgery, but these results are not directly comparable and are often contradictory [4–16].

In Hungary in 2005 a prospective, randomized, multicenter phase III clinical trial was initiated in order to explore the role of preoperative intracavitary high-dose-rate (HDR) BT in the curative treatment of ESCC. This preliminary evaluation of the results obtained in the first 185 patients intends to compare the pathologic complete remission (pCR) rate in patients treated with preoperative intracavitary BT to patients who did not receive preoperative BT (where the tumor was probably eliminated by excision or conization), and thus to assess the efficiency of preoperative BT in the sterilization of the specimen. In this paper we also report the preliminary results regarding local tumor control (LTC), distant metastases free survival (DMFS) and 5 year overall survival (OS). The majority of the patients (n=161) were randomized and treated at the National Institute of Oncology in Budapest, 24 patients were enrolled at the1st Department of Gynaecology and Obstetrics, Faculty of Medicine of the Semmelweis University, the latter patients being treated in collaboration with the Uzsoki Municipal Cancer Center in Budapest, Hungary. The collection of data from the other participating center, the Department of Oncotherapy of the Medical School of the University of Pécs is not yet completed.

Methods and Materials

Study Design

The research protocol was approved by the institutional ethics committees of the participating centers and by the Hungarian Health Scientific Committee in February 2005. Between May 2005 and March 2012, 185 women with operable cervical carcinoma of stage IA2, IB1, IB2, IIA1, IIA2 or proximal IIB (i.e. only the proximal third of the parametrium involved) were enrolled in the study. Eligibility criteria included Karnofsky performance status >70, life expectancy >5 years, and written informed consent of the patient. Before enrollment the following examinations were performed in all patients: physical examination; colposcopy; pathologic examination of the specimen obtained by conization, biopsy or dilatation and curettage; chest X-ray; abdomino-pelvic magnetic resonance imaging (MRI) or computer tomography (CT); cystoscopy if expansion to the urinary bladder, and rectoscopy if expansion to the rectum was suspected. Patients not suitable for radical surgery or who had distant metastases, were not enrolled. The conditions that excluded the participation of the patient in the study are listed in Table 1.

Patients were stratified according to the stage of the disease, and were randomized to receive preoperative HDR BT (arm A) or no preoperative RT (arm B). Patients were

Table 1 Conditions that exclude the participation of the patient in the study

1	Karnofsky PS <70;
2	life expectancy <5 years;
3	inoperable patient due to internal causes;
4	in situ cervical carcinoma (pTis, St. 0);
5	St. I/A1, III/A, III/B, IV/A;
6	St II/B distal (involvement of the distal 2/3 of the parametrium);
7	distant metastases (St. IV/B);
8	unsuitable anatomy for preoperative BT (i.e. deformed uterus, intrauterine length of the applicator <4 cm);
9	increased radiosensitivity (collagen-vascular disease, ataxia-teleangiectasia);
10	any abdomino-pelvic disease in the patient's history that increases the risk of complications of the external pelvic irradiation (i.e. pelvic abscess or inflammation);
11	history of malignant disease (other than basalioma or in situ carcinoma of the skin) in the previous 5 years;
12	pregnancy or breast-feeding;
13	any previous surgical or chemotherapeutical treatment of the cervical cancer in the anamnesis (except the biopsy or conization for the present disease);
14	lack of cooperation of the patient (due to psychiatric or addictive disease) that would make impossible the long-term follow-up of the patient;
15	lack of the necessary diagnostic procedures;
16	lack of written consent of the patient.

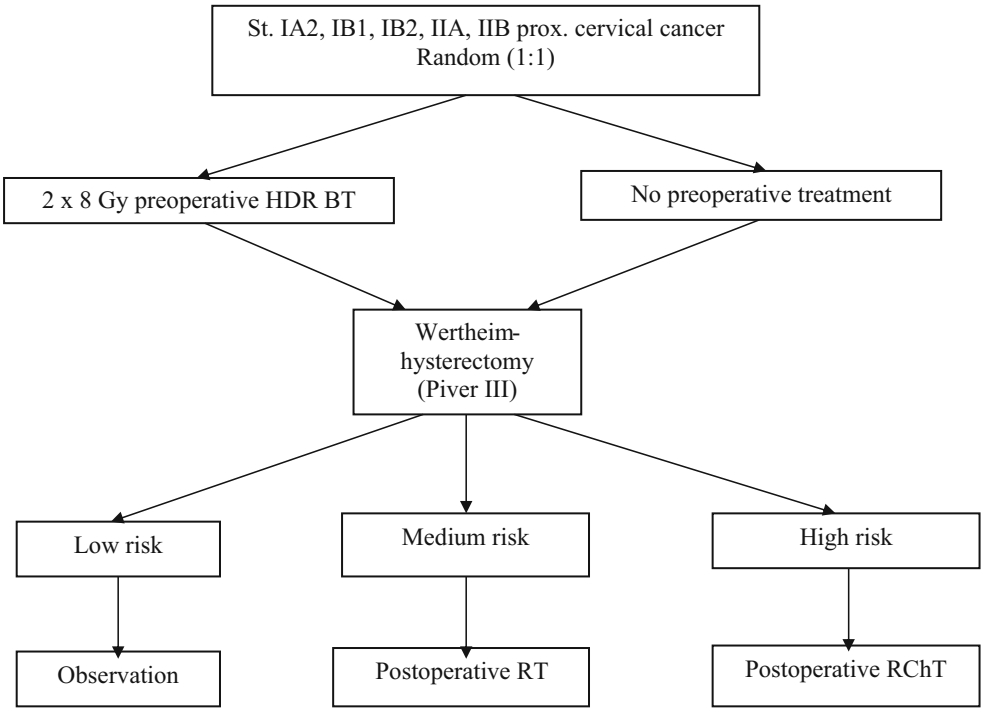

Fig. 1 Scheme of randomization and treatment

randomly allocated in a 1:1 proportion to treatment arms by a sealed-envelope system in blocks of 10. The scheme of randomization and treatment is presented in Fig. 1.

Preoperative Brachytherapy

In arm A preoperative treatment consisted of 2x8 Gy intracavitary HDR BT, with a one-week interval between the two fractions. Fletcher or ring applicator was used with a minimal intracavitary length of 4 cm. The dose was prescribed to point A without dose optimization. In-vivo rectal dosimetry was routinely performed. The surgical intervention was scheduled 10–14 days after the second fraction of preoperative BT.

In arm B no preoperative RT was performed.

Surgery

Surgical intervention in both arms consisted of radical hysterectomy plus bilateral pelvic lymphadenectomy (LAD) (Wertheim, Piver III) with or without additional para-aortic LAD. The surgical protocol was intended to retrieve at least 10 lymph nodes during the intervention. Based on histologic parameters, three risk groups were defined.

Adjuvant Therapy

Postoperative treatment was indicated according to the risk group, based on our institutional treatment protocol. Low-risk patients needed no postoperative treatment. In medium-risk patients combined RT was given: pelvic external beam radiotherapy (EBRT)+BT. High-risk patients received postoperative RChT. (Table 2)

Follow-Up

Patients were followed up at the operating Department of Gynaecology and/or at the Department of Radiotherapy.

Physical examination was performed 4 weeks after the end of the primary treatment, then every 3 months for the first 2 years, and every 6 months thereafter.

Abdomino-pelvic MRI or CT examination was performed first at 6 months, then at 12 months after the end of treatment, and yearly thereafter.

Chest X-ray was performed every year.

Statistical Methods

The primary end-point for this preliminary analysis was the rate of pCR. We also calculated the LTC, DMFS and OS. For survival analysis Kaplan-Meier statistics was used. Differences in outcome between treatment groups were compared with Fisher's exact test. A probability level of 0.05 was considered statistically significant.

Results

The patients' CONSORT flowchart is summarized in Fig. 2. In arm A, 79.5 % of the patients received the allocated

Table 2 Postoperative treatment according to risk groups

Risk groups:	Postoperative treatment:
Low risk: pN0 patients with: −pCR (after BT or conisation) *Or* non pCR, but: −R0 resection and -no parametrium invasion and -tumor size≤4 cm and -LVI neg. and -invasion depth <10 mm and -surgical margin>3 mm and -grade I-II	Observation
Medium risk: pN0, R0 patients, no parametrium invasion, with: −tu. size>4 cm and/or -Grade III tumor and/or -LVI poz. and/or -invasion depth ≥10 mm and/or -surgical margin≤3 mm	RT: 2x7Gy HDR BT+45 Gy pelvic EBRT
High risk: −R1-2 and/or -pN1 and/or -parametrium infiltration	RChT: 2x7 Gy HDR BT+45 Gy pelvic EBRT+weekly 40 mg/m^2 Císplatin i.v. (5–6 series)

pN0 pathologic node negativity, *pCR* pathologic complete remisson, *BT* brachytherapy, *R0* microscopically negative surgical resection, *LVI* lympho-vascular space invasion, *RT* radiotherapy, *HDR BT* high-dose-rate brachytherapy, *EBRT* external beam radiotherapy, *R1* microscopic residual tumor, *R2* macroscopic residual tumor, *pN1* pathologic node positivity, *RChT* radio-chemotherapy, *i.v.* intravenous

treatment, including preoperative BT followed by radical surgery. We excluded from our analysis 18 patients: 2 patients who omitted preoperative BT before surgery, 6 patients who underwent only explorative laparotomy with LAD instead of Wertheim hysterectomy, 3 patients who were not operated at all after the preoperative BT due to the surgeon's decision, and received definitive RChT, one patient in whom liver metastases were identified after the preoperative BT, and 6 patients who quit our Institute, and no further data were available.

In arm B 82.5 % of the patients underwent the planned radical hysterectomy. We had to exclude from analysis 17 patients: in 6 cases only explorative laparotomy+LAD was

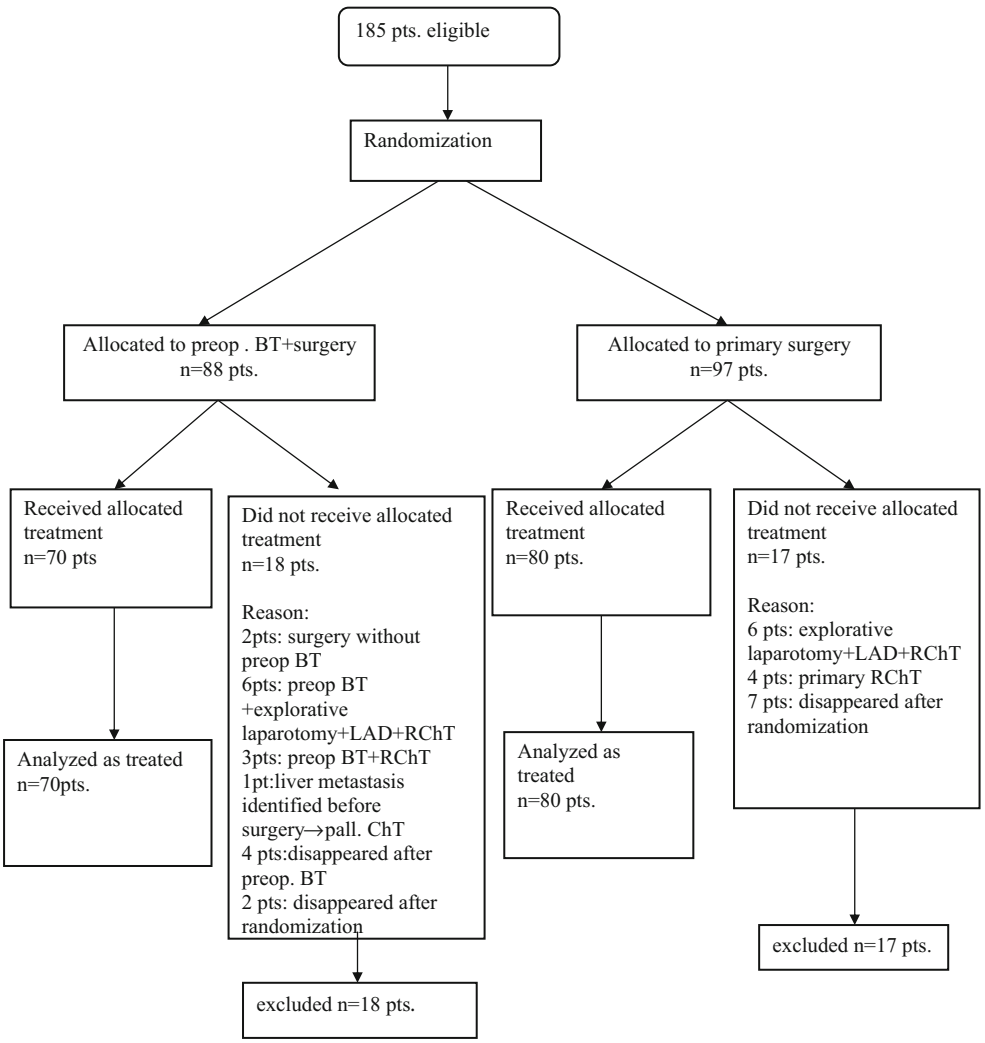

Fig. 2 Patients' CONSORT flowchart diagram

Table 3 Patient and tumor characteristics by treatment arms

Characteristic		All patients (n=150)	Arm A (n=70)	Arm B (n=80)	*p*-value
Mean age (years)		46.9	46.1	47.7	p=0.74
Stage	IA2	6 (4 %)	2 (2.8 %)	4 (5 %)	
	IB1	80 (53.3 %)	39 (55.7 %)	41 (51.3 %)	
	IB2	32 (21.3 %)	15 (21.4 %)	17 (21.3 %)	
	IIA	24 (16 %)	11 (15.7 %)	13 (16.3 %)	
	IIB	8 (5.3 %)	3 (4.3 %)	5 (6.3 %)	
Histology	SCC	119 (79.3 %)	54 (77.1 %)	65 (81.3 %)	
	Adenocc.	26 (17.3 %)	13 (18.6 %)	13 (16.3 %)	
	Mixed	5 (3.3 %)	3 (4.3 %)	2 (2.5 %)	
Nodal status	pN0	109 (72.7 %)	55 (78.6 %)	54 (67.5 %)	p=0.14
	pN1	41 (27.3 %)	15 (21.4 %)	26 (32.5 %)	
Surgical margins[a]	negative	137 (93.2 %)	67 (98.5 %)	70 (88.6 %)	p=0.02
	positive	10 (6.8 %)	1 (1.5 %)	9 (11.4 %)	
Mean tumor size in mm (range) [b]		27.8 (0–70)	25.7 (0–61)	29.3 (0–70)	p=0.28

SCC squamous cell carcinoma

[a] Data on surgical margins were available for 147 patients

[b] Data on tumor size were available for 112 patients

performed, in 4 cases the surgeon countermanded the planned radical hysterectomy and primary RChT was performed, and 7 patients disappeared after randomization. The compliance with the protocol in the two arms was similar. We analyzed altogether 150 histologic specimens.

Patient and tumor characteristics are shown in Table 3.

The mean age of enrolled patients was 46.9 years (range: 23–80 years), with no significant difference between the two treatment arms. The distribution of patients according to clinical stage was also similar in the two arms, more than half of the patients (n=80) being in stage IB1. The histologic type of the tumor in 79.3 % of the cases was squamous cell carcinoma (SCC), the rest were adenocarcinoma (17.3 %) or mixed tumor (3.3 %). The mean number of retrieved lymph nodes in patients who underwent Wertheim hysterectomy was 20 (range: 1 to 61), with the distribution of nodal status showing no significant difference between the two arms. Histologic examination found metastatic lymph nodes in 41 patients (27,3 %). The mean tumor size measured during the histological examination in all patients was 27.8 mm, somewhat smaller in arm A than in arm B: 25.7 mm vs. 29.3 mm (p=0.28). The surgical margins were positive in 1.5 % (1/68) of the cases in arm A, and in 11.4 % (9/79) of the cases in arm B; the difference is significant (p=0.02).

Pathologic complete remission (i.e. no invasive or in situ residual tumor either in the cervix or in the lymph nodes) was found in 18 out of 70 patients (25.7 %) in arm A, and in 9 out of 80 patients (11.2 %) in arm B (p=0.03). The incidence of pCR according to treatment arm and stage is summarized in Table 4. The pCR rate decreased from lower to higher stages. No pCR was registered in stages II/A or II/B.

In the two treatment arms the need for adjuvant treatment established according to the histologic risk group to which the patient belonged was analysed: in arm A 35.7 % of the patients needed no postoperative treatment, only observation being indicated, while in arm B this rate was only 22.5 % (p=0.10). In arm A 31.4 % of the patients needed postoperative RChT, while in arm B 42.5 % of the patients belonged to the high-risk group (p=0.17) (Table 5).

At a mean follow-up of 29 months (range: 1–89 months) only 5 patients developed local recurrence: 3 in arm A and 2 in arm B (p=0.56). The 5-year local tumor control (LTC) is 95 %, the median time of the local recurrence is 7 months (range: 5–29). Ten patients had distant metastases at a median time of 13 months (range 7–30), 6 of them in arm A, 4 in arm B (p=0.43). Three of these patients recurred first locally, and disseminated afterwards. There is no significant difference in OS between the two groups: there were 7 patients lost in both arms, i.e. a 85.2 % and a 81.9 % OS rate in arm A and arm B,

Table 4 Pathologic complete remission (pCR) by treatment arm and stage

	pCR in arm A (preop. BT) (n=70)	pCR in arm B (no preop. BT) (n=80)	pCR in arms A+B (n=150)
IA2 (n=6)	2/2 (100 %)	2/4 (50 %)	4/6 (66 %)
IB1 (n=78)	15/39 (38.5 %)	5/39 (12.8)	20/78 (25.6 %)
IB2 (n=34)	1/15 (6.7 %)	2/19 (10.5 %)	3/34 (8.8 %)
IIA+B (n=32)	0/14 (0 %)	0/18 (0 %)	0/32 (0 %)
All stages (n=150)	18/70 (25.7 %)	9/80 (11.2 %)	27/150 (18 %)

Fisher-exact test: p=0.03

Table 5 Distribution of patients according to histologic risk groups

	Low risk		Medium risk		High risk	
	Arm A (preop. BT)	Arm B (no preop. BT)	Arm A (preop. BT)	Arm B (no preop. BT)	Arm A (preop. BT)	Arm B (no preop. BT)
IA2	2	3	0	0	0	1
IB1	19	12	11	15	9	12
IB2	3	2	7	9	5	8
IIA	1	0	4	3	6	10
IIB	0	1	1	1	2	3
	25/70 (35.7 %)	18/80 (22.5 %)	23/70 (32.8 %)	28/80 (35 %)	22/70 (31.4 %)	34/80 (42.5 %)

preop. preoperative, *BT* brachytherapy

respectively. (p=0.80). (Fig. 3) The 5 year OS for all patients is 83.5 %. There was one patient who developed local recurrence in spite of the negative surgical specimen, and died due to the dissemination of the disease. Thus the OS in the pCR group is 91.8 %, while in the non-pCR group it is 81.5 % (p=0.31) (Fig. 4).

Discussion

In principle, the aim of preoperative RT is to achieve partial or complete pathologic remission of the tumor (downsizing, eventually downstaging), to increase the probability of ablastic surgery, thus decreasing or eliminating the need for adjuvant RT [4,5,9]. We summarized the results of several retrospective studies from the literature regarding the effect of preoperative BT in Table 6. With higher doses (39–75 Gy) of low-dose-rate (LDR) or HDR BT the pCR rate was from 52-88 %, while with lower doses of HDR BT the same proportion was 23–45 % [4,5,8–11,13,17,18]. In certain institutions in more advanced stages (I/B2-II/B) the preoperative treatment is combined RT (tele+brachytherapy), with or without concomitant ChT, followed by adjuvant hysterectomy. The majority of these studies concluded that in patients with pCR obtained by preoperative BT the LTC and the OS was better than in cases that showed minimal or no regression to RT [4,5,7,19].

However, most of the studies that deal with the effect of preoperative RT are retrospective, with no control group, so there is no direct comparison between the results of surgery alone versus preoperative BT followed by surgery. One of the

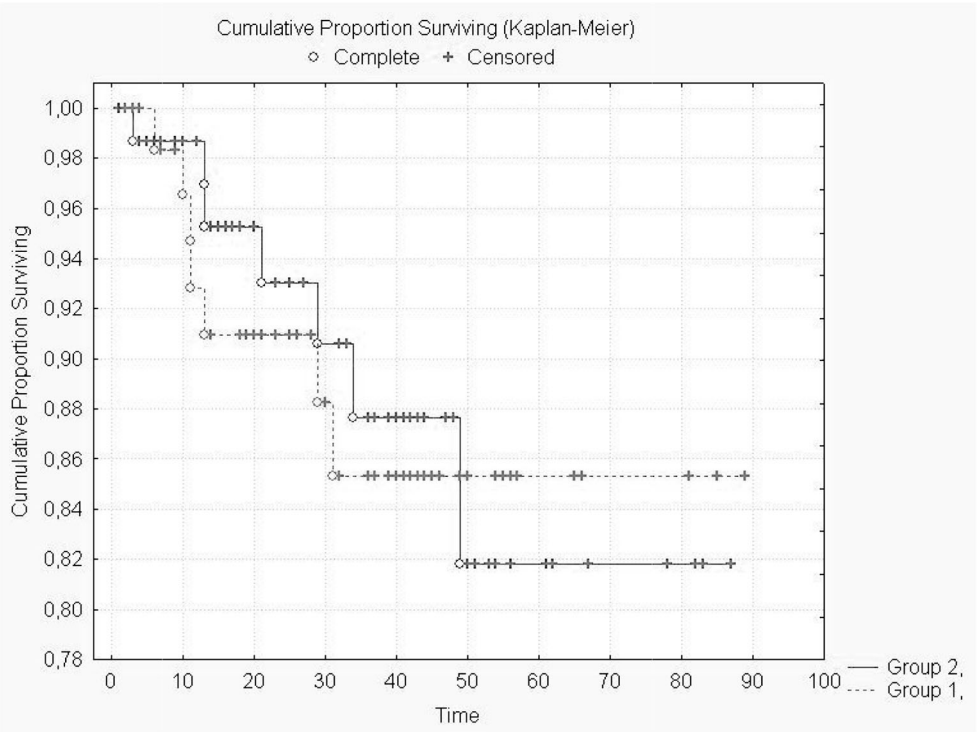

Fig. 3 Overall survival in the two arms. Group 1: with preop. BT, Group 2: no preop. BT; Fisher-exact test: p=0.8

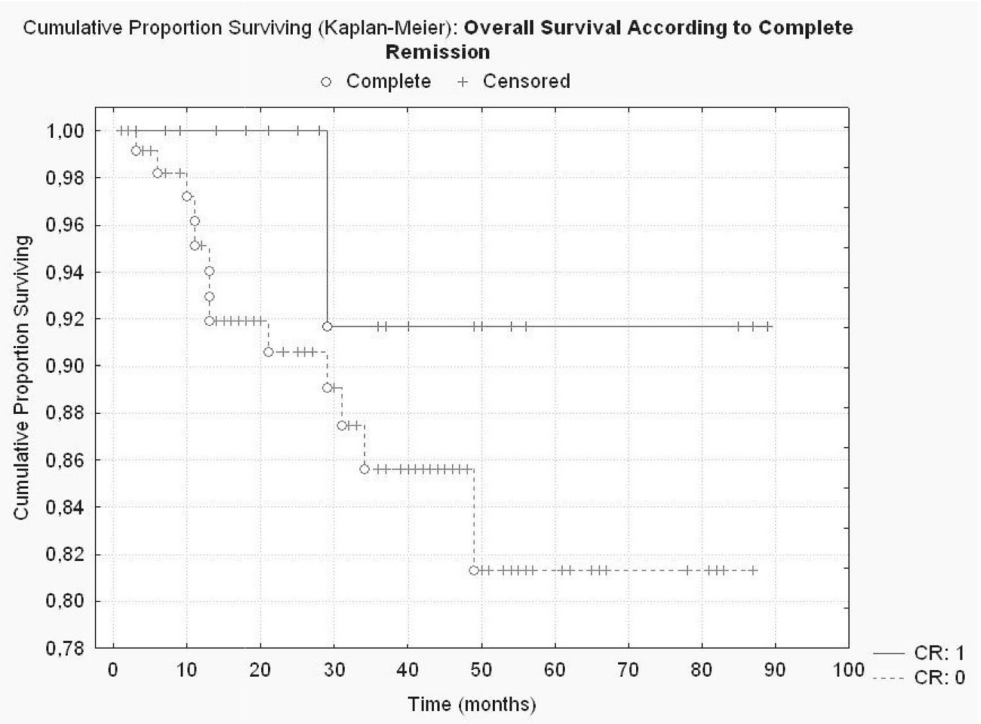

Fig. 4 Time to death from any cause by Kaplan-Meier estimates by pathologic response. *CR:1*=pathologic complete remission; *CR:0*=no pathologic complete remission; Fisher-exact test: p=0.3

few comparative studies was published by the Tenon Hospital from Paris [4]. In their retrospective analysis of 414 patients with cervical cancer stage I/B1, I/B2, II/A and II/B proximal, 246 patients were treated with 65 Gy preoperative LDR BT, while in 168 patients 45–50 Gy postoperative pelvic EBRT was delivered and/or 20–50 Gy vaginal LDR BT. From the group of patients treated with preoperative BT only the high-risk patients (R1 resection, node positive status, lymph node

Table 6 The rate of pathologic complete remission, local tumor control and overall survival in series using preoperative intracavitary brachytherapy

Institute	Stage	n	FUP (yrs)	Preoperative RT	pCR (%)	5-year LTC (%)	5-year OS (%)
Radiumhemmet, Stockholm [5]	IB-IIA	121	6	45 Gy LDR BT	79	98 (pCR) 46 (non-pCR)	95 (pCR) 46 (non-pCR)
IGR, Paris [6]	IB-IIB	441	>7	60 Gy LDR BT	NR	86	87
IGR, Paris [16]	IB1	39	NR	60 Gy LDR BT	60	86	94
IGR, Paris [8]	IA2-IIIB	33	NR	60 Gy LDR BT; 45 Gy EBRT+15 Gy LDR BT	55	NR	NR
IGR, Paris-Lille [24]	IB1	162	3	60Gy	75	94	95
Tenon Hospital, Paris [4]	IB1-IIB	246	9	50-75 Gy LDR BT	72	94 (pCR) 76 (non-pCR)	89 (St. IB1) 61 (St. IB2) 63 (St. IIA) 47 (St. IIB)
Tenon Hospital, Paris [7]	IB2-IIB	62	4	40.5 Gy EBRT+CT+20 Gy LDR BT	63	92 % (pCR) 67.5 % (non-pCR)	78
Marseille [9]	IA2-IIA	192	5	60 Gy LDR BT	71	96	91
Nice [17]	IB1-IIA1	32	2	39Gy HDR BT in 9 fractions	88	NR	NR
Chicago, USA [20]	IB-IIA	43	4.5	45 Gy LDR BT	22	97	95 (pCR) 78 (non pCR)
Sao Paulo [19]	IIB	67	6	45 Gy EBRT+12 Gy HDR BT	40	96 (pCR) 86 (non-pCR)	72 (pCR) 54 (non-pCR)
Gliwice [18]	IB-IIA	139	8	30-45 Gy HDR BT	60	NR	93 (St. I/B) 89 (St. II/A)
HNIO, Budapest [12]	IB	60	NR	1 x 7 Gy HDR BT	45	NR	NR
Semmelweis University, Budapest [13]	IA2-IIB	501	>5	2 x 5.5 Gy HDR BT	23	NR	94 (pCR) 66 (non-pCR)
Recent study	IA2-IIB	150	2.5	2 x 8 Gy HDR BT	26	95	83

FUP=follow-up period; *RT*=radiotherapy; *pCR*=pathologic complete remission; *LTC*=local tumor control; *OS*=overall survival; *LDR*=low-dose-rate; *BT*=brachytherapy; *IGR*=Institut Gustave Roussy; *NR*=not reported; *EBRT*=external beam radiotherapy; *HDR*=high-dose-rate; *NR*=not reported; *HNIO*=Hungarian National Institute of Oncology

invasion or residual tumor above 4 cm) received 45 Gy postoperative pelvic EBRT. The pCR rate after preoperative BT was 72 %, but the sequence of RT (preoperative vs. postoperative) did not influence the survival rates. However, the pCR obtained after preoperative BT was an independent, significant predictor for 5-year DFS (93 % in pCR vs. 71 % in non-pCR patients; $p<0.001$.) Another factor that significantly influenced the relapse free survival was the size of the residual tumor (more or less than 1 cm). The analysis of late side effects showed that preoperative BT did not raise the number of grade 3–4 complications, while the postoperative pelvic EBRT significantly raised the proportion of severe side effects (22 % vs. 7 %; $p=0.0002$)

PCR obtained by preoperative BT was also found by a Swedish group from Stockholm as being a strong prognostic factor for long-term survival [5]. They made a retrospective analysis of 121 patients in stage IB-IIA, treated in the Radiumhemmet with a total dose of 40–45 Gy in 2 fractions. Radical surgery was performed 4 weeks after BT. Node-positive or R1 patients received postoperative EBRT. The pCR rate was 79 %. The 5-year OS in patients with pCR was 95 %, while in patients with residual tumor it was only 46 % ($p<0.0001$). Within node-negative patients in the pCR group the 5-year OS was as high as 98 %, compared with 64 % registered for node-negative, non-pCR patients ($p<0.0001$). At a median follow-up (FUP) of 71 months loco-regional relapses were registered in 2 % of the patients with pCR, compared to 54 % of the patients with non-pCR.

In spite of the publications that support preoperative RT, in Anglo-Saxon countries primary surgery is favoured [1,2]. However, there has been positive experience with the use of preoperative BT in the USA as well. Mundt et al. [20] treated 43 cervical cancer patients in stages I/B-II/A, with tumor size >2 cm with 45 Gy preoperative LDR BT, followed by hysterectomy after 25 days. The surgical specimen was tumor free in 22.5 % of the patients. Local pelvic recurrence occurred in only one patient, who did not receive the whole dose of BT due to a febrile episode. They found nodal involvement to be the most important prognostic factor for the DFS ($p<0.0004$), but there was a tendency for better DFS in patients with pCR or only focal microscopic residual disease at the time of surgery. ($p=0.18$)

According to the literature, after radical hysterectomy alone we can expect the recurrence of the disease in 15 % of the patients, a quarter of these being represented by central pelvic recurrences [21–23]. Preoperative BT performed in selected patients could have an important role in the prevention of these recurrences.

In Hungarian clinical practice in the treatment of early-stage cervical cancer preoperative BT has been routinely used beginning in the 1960's, first with LDR, later on with HDR BT [10–12,14]. In a retrospective study published by the Uzsoki Municipal Cancer Center in 2004, with 2x5.5 Gy preoperative HDR BT delivered to 153 patients in stage I/B a pCR rate of 33.4 % was obtained [10]. According to their experience, 2x5.5Gy can be delivered without the risk of severe complications. Németh [12] reported a 45 % pCR rate in 60 patients in stage I/B, who received 1x7 Gy HDR BT. In our study, in spite of the higher dose (2x8Gy) of preoperative BT, the pCR rate is somewhat lower (25.7 %), which can be explained by the fact that we enrolled patients in stage II/A and II/B proximal as well ($n=32$), and in none of these cases pCR was obtained. If we look at patients in stage I/A2-I/B2, who received preoperative BT, the pCR rate is 32.1 %, while looking at stages I/A2-I/B1 the same rate is 41.4 %. Papp et al. [13] noted a 23 % pCR rate in 501 patients in stages I/A2-II/B, treated with preoperative BT and Wertheim hysterectomy, a result similar to ours.

The preliminary results of our prospective, randomized, multicenter study show that preoperative HDR BT can play an important role in the sterilization of the surgical specimen, as it increased the rate of tumor-free specimen from 11.2 % to 25.7 %. In arm B, where no preoperative treatment was delivered, the tumor was probably eliminated during the diagnostic excision or conization.

Comparing the mean tumor size in the two treatment arms in patients who had measurable residual tumor, we found that in the group that received preoperative BT the mean tumor size was somewhat smaller than in the surgical arm (25.7 mm versus 29.3 mm). Though the difference is non-significant, the downsizing effect of preoperative BT is highly probable, and with higher doses we might expect a more pronounced difference. According to the above mentioned French study [4] the size of the residual tumor significantly influenced the relapse-free survival (RFS), so by downsizing the tumor we can theoretically expect a better prognosis.

The positivity of the surgical margins is another important risk factor for local failure and indicates the need for aggressive postoperative treatment. We compared the positivity of surgical margins in the two treatment arms, and found a significant difference in favor of the preoperative BT arm. (1.5 % versus 11.4 %; $p=0.02$). This result also supports the idea that with preoperative BT we can theoretically expect better LTC, and we can lessen the need for adjuvant treatment. By checking the indications for adjuvant treatment in our patients, we found that after preoperative BT we could avoid postoperative EBRT in 37.2 % of the cases, which is 13,2 % more than without preoperative treatment. At the same time, the rate of high-risk patients who needed postoperative RChT was 11.1 % less in the pre-irradiated arm. Other studies [4,5,9] also support the idea that with preoperative BT in some of the patients postoperative pelvic irradiation, responsible for most of the bladder and bowel complications, can be spared. In a series of 162 cases of stage IB1 cervical cancer treated with 60Gy preoperative utero-vaginal BT followed by laparoscopic radical hysterectomy (LRH) [24], the need for postoperative adjuvant RChT was

7 %, compared to 24 % in the series reported by Pellegrino et al. [25], including exclusively stage IB1 disease, or 66 % reported by Puntambekar et al. [26], including stage IA2 and IB1 patients, who underwent LRH and pelvic LAD.

In spite of the positive experience, it is still controversial whether or not preoperative BT, through the pCR induced, improves the tumor-free and/or overall survival. In 1995, the Medical University of Debrecen published the retrospective analysis of 324 cervical cancer patients in stage I/B-II/A, from which 227 patients received preoperative BT [14]. According to their results, preoperative treatment did not improve the survival rates. Since this was not a randomized trial, we cannot consider these results as strong evidence.

In our series the OS was better in the pCR group than in the non-pCR group (96.1 % versus 89.3 %), but the difference is non-significant at the moment, with a longer follow-up needed to appreciate this effect.

In 2009, the Institut Gustave Roussy published the dosimetric and clinical results of 39 patients, mostly in stage I/B1, who received 60Gy preoperative MRI-based LDR BT [16]. The histologic examination showed pCR in 60 % of patients. Node-positive patients received postoperative RChT. The 4-year OS was 94 %, DFS was 86 %. Considering the excellent LTC and the low toxicity obtained with this treatment modality, they expressed the need for a randomized study which would compare the results of primary surgery versus surgery following preoperative BT.

Conclusions

To our knowledge this is the first prospective randomized clinical study demonstrating that preoperative BT significantly increases the rate of pCR and the rate of negative surgical margins. There is no difference in the compliance with the treatment between the two arms. Preoperative BT seems to diminish the tumor size and the need for aggressive postoperative treatment and to improve OS in the pCR group, but these differences are not significant. However, the mean follow-up period is only 29 months in our study. Longer follow-up is needed to establish whether the increased rate of pCR will translate into better local tumor control and/or long-term survival.

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