Survival and toxicity of radical radiotherapy (with or without brachytherapy) for FIGO Stage I and II cervical cancer: a mono-institutional analysis

L. Bandera[1], B. La Face[1], C. Antonioli[1], M. Galelli[2], B. Ghedi[2], A. Fiume[2], M. Buglione[1], S. M. Magrini[1], E. Sartori[3]

[1]Istituto del Radio O. Alberti, Department of Radiation Oncology, Spedali Civili Hospital and Brescia University, Brescia
[2]Department of Medical Physics, Spedali Civili Hospital, Brescia
[3]Department of Obstetrics and Gynecology, Spedali Civili and Brescia University, Brescia (Italy)

Summary

Purpose of investigation: To add to the existing outcome data regarding radical radiotherapy (RT) for FIGO Stage I and II cervical cancer in a mono-institutional series and to evaluate the cost-benefit ratio of the addition of brachytherapy (BRA) to external-beam radiotherapy (EBRT). *Materials and Methods:* The authors report on 240 patients (pts) with FIGO Stage I and II cervical cancer, consecutively treated with radical RT from 1990 through 2009 at the Istituto del Radio "O. Alberti" (EBRT alone, 32, EBRT and BRA, 189, BRA alone, 19). BRA was delivered with low dose rate (LDR, 133.64%) until 2003 and then with high dose rate (HDR, 75.36%). RT was associated with concomitant chemotherapy (CHT), mainly weekly cisplatin 40 mg/m^2, in 87 pts, mostly after 2000. The Chi-square test was used to compare the different variables, the Log-Rank test to compare the actuarial survival values, and the Cox-model for the multivariate analysis. *Results:* Five-year actuarial overall survival (OS) equalled 65%, disease specific survival (DSS) 77%. Regardless of disease stage, better DSS was evident in pts treated with EBRT and BRA compared with those treated with EBRT alone (82% and 58% respectively, $p = 0.005$); pts treated with concomitant CHT (dose intensity $\geq 50\%$) and higher RT doses (RT cumulative EQD2 ≥ 75 Gy) obtained better DSS. Complete response (CR) rate approached 88.4% (206/233 evaluable pts) and more than half of the subsequent failures (21/36) were in distant sites. Older patients and those given BRA had better OS and DSS, while BRA dose rate did not result related with these outcomes. Chronic G3/G4 toxicity involved more frequently the intestinal/rectal tract than other organs at risk. Rectal and vaginal serious chronic sequelae developed mainly in pts treated with EBRT and BRA and suggest the need for more advanced treatment techniques. *Conclusions:* the present mono-institutional analysis confirms the efficacy of radical RT for the treatment of cervical cancer and provides support to the role of BRA to obtain better outcomes. An effort to reduce long term toxicity of the treatment is needed.

Key words: Cervical cancer; Radical radiotherapy; Brachytherapy.

Introduction

Cervical cancer represents the third most frequent cancer site among women. For early-stage disease, survival outcomes of surgery and radiotherapy (RT) are known to be similar. Locally advanced carcinoma of the cervix should be treated with a combination of external-beam radiotherapy (EBRT) and intracavitary RT (brachytherapy-BRA). Since 1999, concurrent chemotherapy (CHT) with radiation has been the standard of care in the treatment of cervical cancer. [1-7]

BRA is a kind of conformal dose escalation and plays an essential role for its ability to deliver very high doses to the tumour, decreasing the risk of residual cancer and of pelvic relapse. [8-9] Low-dose-rate (LDR) BRA has been in use for the treatment of cervical cancer for nearly a century, although the method has been greatly refined, while high-dose-rate (HDR) BRA has been in use for over 30 years. HDR and LDR BRA seem to be equivalent treatments in terms of survival outcomes. [10-14]

In this study the authors retrospectively analyzed the survival outcomes and the treatment-related toxicity for women with cervical cancer treated with radical RT at the present Institution. The authors' aim is to establish a historical benchmark database to assist in identifying possible pathways to improve results taking advantage of the technical and clinical advancements in dose planning and delivery, both for BRA and for EBRT.

Materials and Methods

Between 1990 and 2009, 247 patients (pts) affected by cervical cancer (FIGO Stage I and II, any N) were treated with radical-exclusive RT (+/- concomitant CHT) at the "Istituto del Radio O. Alberti" – Radiation Oncology Department of the Brescia University: seven of them were excluded for the lack of any information after treatment, leaving 240 pts available for the analysis. All the data were retrospectively collected from the clinical records; if no information was available, patient's vital status was defined through the municipality of residence or directly by telephone interview; as far as the evaluation of chronic sequelae and the maintenance of tumour control are concerned, pts examined only once after treatment were judged

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Table 1. — *Patient features.*

Age	
< 60 yrs	74 (30.8%)
≥ 60 yrs	166 (69.2%)
IK	
60 - 70	15 (6.3%)
80 - 90 - 100	225 (93.7%)
Comorbidities	
Yes	160 (66.7%)
No	80 (33.3%)

**Diabetes 4.2% (DM), hypertension 25.4% (HY), obesity 5% (OB), DM+HY 5.8%, DM+OB 0.4%, HY+OB 3.3%, DM+HY+OB 2.9%, other 19.6%*

"lost at follow up". In the absence of further information, pts alive at least eight years after treatment were judged "alive without disease". The median effective follow up was 1,695 days (average 2,048). Clinical response to the treatment was assessed at least six months after the end of treatment, using diagnostic imaging (ultrasonography (US), computed tomography (CT) or magnetic resonance imaging (MRI) +/- biopsy in case of doubtful persistence of disease) and/or clinical examination.

Pts and disease features are shown in Tables 1 and 2. The authors analysed distinctly the disease features of the first and the second decade considered because in the last years the present Institution modified the diagnostic protocols used for staging, according to the improvement of diagnostic imaging techniques, and to the their increasing availability. Staging included clinical examination alone in nine pts, CT in 79 pts, MR (+/-CT) in 139 pts, and CT positron emission tomography (CT-PET) (+/- MR) in 13 pts: MR and CT-PET were mostly used after 2000, while CT was the main procedure used until 1999. Along with an increased use of more accurate imaging techniques, a higher proportion of patients with advanced clinical stage was also registered after the year 2000: the new techniques allowed to detect more efficiently any parametrial invasion or nodal involvement, adding information about pelvic and para-aortic nodes and the metabolic activity of the suspected disease sites (Tables 3-5).

Thirty-two pts were treated with EBRT alone because cervical anatomical characteristics did not enable a correct implant for BRA boost or for poor general conditions: the dose to the pelvis was 45-50 Gy, while the tumour was boosted to higher doses reaching a total dose of 66 Gy or more in 56.3% of cases. Nineteen pts were treated with BRA alone (14 LDR BRA, five HDR

Table 2. — *Disease features.*

	1990-1999 93 pts	2000-2009 147 pts	Entire series 240 pts
Histology			
Squamous	68 (73.1%)	119 (81.0%)	187 (77.9%)
Adeno	8 (8.6%)	10 (6.8%)	18 (7.5%)
Adenosquamous	3 (3.2%)	7 (4.8%)	10 (4.2%)
Other	13 (14.0%)	11 (7.5%)	24 (10.0%)
Unknown	1 (1.1%)	0 (-)	1 (0.4%)
Grading			
G1	6 (6.5%)	14 (9.5%)	20 (8.3%)
G2	35 (37.6%)	48 (32.7%)	83 (34.6%)
G3	34 (36.6%)	40 (27.2%)	74 (30.8%)
G4	0 (-)	3 (2.0%)	3 (1.3%)
Gx	18 (19.3%)	42 (28.6%)	60 (25.0%)
FIGO Stage			
IA	1 (1.1%)	0 (-)	1 (0.4%)
IB1	18 (19.4%)	19 (12.9%)	37 (15.4%)
IB2	5 (5.4%)	10 (6.8%)	15 (6.3%)
IIA	37 (39.7%)	30 (20.4%)	67 (27.9%)
IIB	32 (34.4%)	88 (59.9%)	120 (50.0 %)
Pelvic nodes			
N0	86 (92.5%)	118 (80.3%)	204 (85.0%)
N1	5 (5.3%)	28 (19,0%)	33 (13.8%)
Nx	2 (2.2%)	1 (0.7%)	3 (1.2%)
UICC stage			
I	23 (24.7%)	27 (18.4%)	50 (20.8%)
IIA	35 (37.6%)	28 (19.0%)	63 (26.3%)
IIB	30 (32.3%)	63 (42.9%)	93 (38.7%)
IIIB	5 (5.4%)	29 (19.7%)	34 (14.2%)

Table 5. — *Staging procedures applied in the different stage groups (N category) (p = 0.00).*

	Nx	N0	N1	TOT
Clinical exam/ biopsy	0 (-)	9 (100%)	0 (-)	9 (100%)
CT	0 (-)	75 (94.9%)	4 (5.1%)	79 (100%)
MR (+/- CT)	3 (2.2%)	113 (81.3%)	23 (16.5%)	139 (100%)
CT-PET (+/-MR)	0 (-)	7 (53.8%)	6 (46.2%)	13 (100%)
TOT	3 (1.3%)	204 (85%)	33 (13.8%)	240 (100%)

Table 3. — *Changes in staging procedures in the two subsequent accrual periods.*

	Clinical exam	CT	MR (+/- CT)	CT-PET (+/-MR)	TOT
1990-1999	7 (7.5%)	56 (60.2%)	30 (32.3%)	0 (-)	93 (100%)
2000-2009	2 (1.4%)	23 (15.6%)	109 (74.1%)	13 (8.9%)	147 (100%)
TOT	9 (3.8%)	79 (32.9%)	139 (57.9%)	13 (5.4%)	240 (100%)

Table 4. — *Staging procedures applied in the different stage groups (T category) (p=0.00).*

	T1a	T1b1	T1b2	T2a	T2b	TOT
Clinical exam/ biopsy	1 (11.1%)	4 (44.4%)	0 (0%)	3 (33.3%)	1 (11.1%)	9 (100%)
CT	0 (-)	13 (16.5%)	5 (6.3%)	33 (41.8%)	28 (35.4%)	79 (100%)
MR (+/- CT)	0 (-)	19 (13.7%)	10 (7.2%)	29 (20.9%)	81 (58.3%)	139 (100%)
CT-PET (+/-MR)	0 (-)	1 (7.7%)	0 (-)	2 (15.4%)	10 (76.9%)	13 (100%)
TOT	1 (0.4%)	37 (15.4%)	15 (6.3%)	67 (27.9%)	120 (50%)	240 (100%)

Table 6. — *Point A EQD2 for the pts of the entire series. Of the pts treated with BRA alone (19 pts), 14 were given 70 Gy EQD2, one was given 59.5 Gy EQD2, three were given 48 Gy EQD2, and one was given 43 Gy EQD2.*

EQD2	< 60 Gy	60-69 Gy	70-74 Gy	75-79Gy	≥ 80 Gy	TOT
BRA LDR	0 (0%)	0 (0%)	40 (30.1%)	24 (18%)	69 (51.9%)	133 (100%)
BRA HDR	5 (6.7%)	2 (2.7%)	3 (4%)	14 (18.7%)	51 (68%)	75 (100%)
NO BRA (EBRT alone)	4 (12.5%)	20 (62.5%)	8 (25%)	0 (0%)	0 (0%)	32 (100%)
TOT	9 (3.8%)	22 (9.2%)	51 (21.3%)	38 (15.8%)	120 (50%)	240 (100%)

Table 7. — *Clinical response (p = 0.6).*

Clinical Response	All Cases	EBRT + BRA	EBRT alone	BRA alone
Complete response	206/233 (88.4%)	172/186 (92.5%)	17/30 (56.7%)	17/17 (100%)
No long term follow up	4	4	–	–
- CR mantained	166/202 (82%)	139/168 (83%)	15/17 (88.2%)	12/17 (70.6%)
- Recurrence in the tumour site	9/202 (4.5%)	8/168 (5%)	1/17 (5.9%)	0/17 (-)
- Recurrence in the pelvis	6/202 (3%)	4/168 (2%)	1/17 (5.9%)	1/17 (5.9%)
- Distant metastases (mainly lung and bone)	21/202 (10.5%)	17/168 (10%)	0/17 (-)	4/17 (23.5%)
Partial response	21/233 (9.1%)	13/186 (7%)	8/30 (26.6%)	0/17 (-)
Non response	2/233 (0.8%)	1/186 (0.5%)	1/30 (3.4%)	0/17 (-)
Disease progression	4/233 (1.7%)	0/186 (-)	4/30 (13.3%)	0/17 (-)

BRA) because they were very old women (13 pts), because they were affected by early stage disease (three pts) or for important comorbidities (three pts). The remaining 189 were treated both with pelvic EBRT and BRA; the BRA boost (119 LDR BRA, 70 HDR BRA) allowed to reach higher doses to the tumour for the majority of pts: from 1990 to 2003 BRA was delivered with LDR (64%), then with high dose rate (HDR) (36%) up to a point-A cumulative dose of 80 Gy (EQD2) or more for the majority of them (Table 6).

The pelvis (including the tumour and the obturator, internal iliac, external iliac, common iliac, and pre-sacral lymph nodes, with cranial limit between L4 and L5) was irradiated mainly with a four-box-field technique (206 pts); the two-fields technique (AP-PA) was used for six pts; for nine pts the EBRT technique was not specified in the clinical records. Until 1997 a 2D-planned RT (46 pts), was utilized, then a 3D-conformal 3D RT became the standard (175 pts). Pathologic pelvic nodes were treated with a boost delivered with EBRT, after calculation of the dose received with BRA (using point-B as reference point). Concomitant CHT was administered only to 87 pts: the majority (92%) was treated with weekly cisplatin (40mg/m^2), but only 33.8% of them received CHT with dose intensity ≥ 50%, mainly because of hematologic or gastrointestinal acute toxicity; a significant difference was however recorded between the first and the second decade: in fact, after 2000, concomitant CHT became the standard treatment. Moreover, in this period, higher RT doses were delivered to the tumour, thanks to the use of 3D-CT for treatment planning and to a more careful use of supportive care therapies. Chronic sequelae were reported according to CCTAE v4.0 scales.

The different variables were compared using the Chi-square test; the authors used the Log-Rank test to analyse the actuarial survival values, assuming as significant a *p*-value of less than 0.05, and the Cox-model for the multivariate survival analysis. The variables entered in the initial Cox-model were those with a *p*-value greater than 0.05 and those clinically significant. All the analyses were performed with the statistical software SPSS 17.0.

Results

The clinical response to treatment is shown in Table 7 (the table does not consider the seven pts without clinical information after treatment); the median EQD2 was 82 Gy for pts who reached CR (average value 77.7 Gy, range 40-98 Gy) and 71 Gy for those with partial response, non response or disease progression (average value 71 Gy, range 54-85 Gy). Overall survival (OS) at five and ten years was respectively, 65% and 51% while disease specific survival (DSS) was 77% at five years and 73% at ten years: disease related deaths occurred in fact mainly within three years after the end of treatment.

In the present series, prognosis seems to be more related to the type of treatment received than to the stage of disease: with some limit, related to the non-homogeneity of the sample, better results were reached in women treated both with EBRT and BRA compared with those treated with EBRT alone (five years DSS 80% vs. 58%, $p = 0.00$), regardless of the stage of disease (Figure 1). Women treated with high radiotherapy doses obtained better outcomes, also if they were affected by more advanced disease: five years DSS was 83.5% for pts treated with EQD2 >=75 Gy and 66% for pts treated with EQD2 <75 Gy ($p = 0.014$); analyzing this variable only for FIGO IIB diseases five years DSS was 84% and 58%, respectively ($p = 0.003$). Better results were obtained for pts treated with both RT and CHT in comparison to those treated only with RT, but when the cumulative dose delivered was lower than 75 Gy the advantage of CHT decreased: five years DSS was 85% for pts treated with CHT+RT ≥ 75 Gy EQD2, 78% for pts treated with RT ≥ 75 Gy, without CHT, 60% for pts treated with CHT+RT< 75 Gy, and 59% for pts treated with RT< 75 Gy without CHT ($p= 0.047$) (Figure 2).

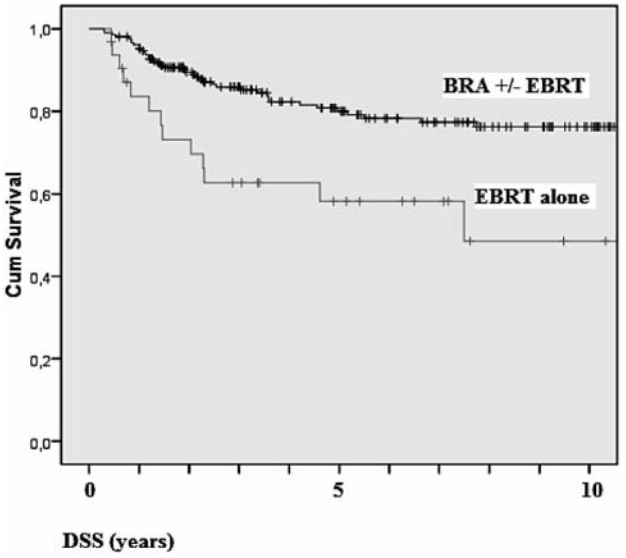

Figure 1 – DSS for the different treatment groups (EBRT alone vs. BRA+/-EBRT).

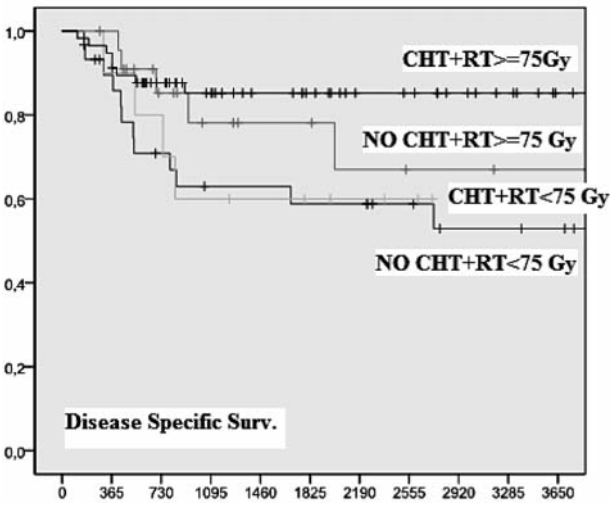

Figure 2 – DSS according to the treatment received.

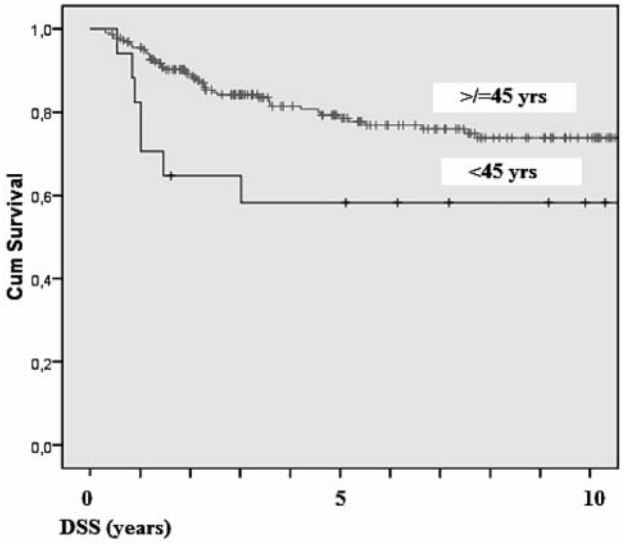

Figure 3 – DSS and patients age ($p = 0.04$).

Table 8. — *Multivariate analysis of disease specific survival.*

		p-value	Exp (B)
Age	< 60 yrs	0.06	1
	> 60 yrs		0.581
Treatment	EBRT + BRA	0.00	1
	BRA alone		1.841
	EBRT alone		2.805

Among pts treated with BRA (+/- EBRT), no significant differences in OS and DSS rates were found according to the different dose rates; a CR was achieved in 89.5% of pts treated with LDR-BRA and in 93.3% of pts treated with HDR-BRA ($p = 0.18$).

Older pts had better outcomes than younger ones regardless of the stage of disease, of histological features or treatment received (data not shown); women younger than 60 years had worse outcomes than older ones (five-year DSS 81% vs. 68%, $p = 0.083$): this difference was more evident for women younger than 45 years (five-year DSS 78.5% vs. 58.2%, $p = 0.04$) (Figure 3).

At multivariate survival analysis, only combined treatment (EBRT + BRA) was confirmed to be a significant variable determining better DSS ($p = 0.00$) (Table 8).

The majority of pts did not develop any chronic toxicity; the majority of G4 chronic sequelae, mainly arose within three years after treatment, involved the intestine or rectum (13 cases), as mucosal ulcerations/fistula or bowel occlusions implying temporary or definitive bowel diversion; three patients underwent pielostomy for bladder perforation, one patient developed pelvic fibrosis. Among G3 sequelae, hemorrhagic proctitis requiring laser-coagulation or transfusion for anaemia was experienced in 20 pts, two

Table 9. — *Different kinds of toxicities may coexist in the same patient.*

	Chronic toxicity					
	Hematopoietic system	Rectum/ intestine	Urinary trait	Skin	Pelvis	Bone
G0	222	125	178	221	114	222
G1	1	39	27	1	51	0
G2	0	26	13	1	50	0
G3	0	20	2	0	7	1
G4	0	13	3	0	1	0
Gx	17	17	17	17	17	17
	240	240	240	240	240	240

Table 10. — *Rectal toxicity and radiotherapy dose (p = 0.02).*

Rectal-enteric toxicity	< 75 Gy EQD2 (82 pts)	≥ 75 Gy EQD2 (158 pts)	Tot
G0	50/82 (61%)	75/158 (47.5%)	125/240 (52.1%)
G1-G2	16/82 (19.5%)	49/158 (31%)	65/240 (27.1%)
G3-G4	7/82 (8.6%)	26/158 (16.4%)	33/240 (13.7%)
GX	9/82 (11%)	8/158 (5.1%)	17/240 (17.1%)

pts had hemorrhagic cystitis requiring hospitalization, seven pts developed vaginal narrowing that enabled physical examination, one patient experienced a pubic fracture due to radio-osteonecrosis two years after treatment. Regarding less severe sequelae (G1-G2), intermittent hemorrhagic proctitis was the more common disorder along with increased bowel frequency, urinary urgency, and vaginal substenosis (G2) or hypotrophy (G1) (Table 9).

Rectal-enteric chronic toxicity developed mainly in pts treated with higher RT doses (Table 10) and in pts treated both with EBRT and BRA: 28.6% of pts treated with the combined treatment experienced G1-G2 toxicity vs. 15.8% of pts treated with BRA alone and 25% of pts treated with EBRT alone, G3-G4 toxicity developed in 16.4% of pts treated with EBRT+BRA and in 6.3% of pts who received EBRT alone (no G3-G4 rectal *sequelae* were registered in pts treated only with BRA)($p = 0.031$). BRA delivered with HDR seemed to be associated with a higher frequency of G3-G4 rectal sequelae if compared to LDR (22.7% vs. 10.5%, $p = 0.004$).

All the vaginal stenosis and 92% of the vaginal substenosis developed in pts treated both with EBRT and BRA, while the frequency of vaginal hypotrophy of pts who received the combined treatment overlaps that of pts treated with BRA alone or with EBRT alone ($p = 0.002$); no differences were found between HDR and LDR. Analyzing distinctly the two decades, we registered more chronic urinary and enteric-rectal G4 toxicities in pts treated between 1990 and 1999: 66.7% of G4 urinary sequelae vs. 33.3% ($p = 0.006$) and 53.8% of G4 enteric-rectal *sequelae* vs. 46.2% ($p = 0.016$); G3 urinary *sequelae* (two cases) developed in pts treated before 2000, while G3 enteric-rectal sequelae developed mainly after 2000 (35% in the first decade vs. 65% in the second decade, $p = 0.016$). Also as far as pelvic toxicity is concerned, the authors registered less toxicities after 2000: 43% of pts did not develop any toxicity in the first treatment period vs. 50.3% in the second one; vaginal stenosis (G3) and substenosis (G2) arose mainly in pts treated before 2000 (G3, 4.3% vs. 2%; G2, 22.6% vs. 19.7%) while mucosal vaginal hypotrophy (G1) was the main side effect registered after 2000 (17.2% in the first decade vs. 23.8% in the second decade) ($p = 0.05$). The authors found no significant statistical correlation between the development of serious chronic *sequelae* and the association with concomitant CHT.

Discussion

As for other retrospective studies, the present analysis presents some limitation: the non-homogeneous features of the sample, the different staging procedures, and the variability of treatment (in terms of planning, dose-prescription, and delivery techniques); another limitation is the lack of homogeneous follow up procedures, since the selection of suitable exams plays a crucial role to evaluate the tumour response and the effectiveness of treatment. Nevertheless the data demonstrated satisfying results in terms of DSS and local control: the use of BRA boost to EBRT is fundamental, since pts who received the combined treatment (EBRT + BRA) had better outcomes than the others. The authors recorded few local relapses and found that distant metastasis were the more common manifestation of recurrence, especially in the first period analyzed: this fact is probably due to the increasing use, in the second decade, of imaging techniques (CT, MRI, CT-PET) that allowed to better define the disease extension, reserving more aggressive treatments to more advanced diseases. Although clinical examination still represents the main staging procedure for cervical cancer evaluation, it is now mandatory to make use of adequate and standardized staging procedures, including MRI to better define soft tissue characteristics and CT/CT-PET to evaluate lymph-nodes status and/or disease systemic extension [15-17].

In this univariate analysis the authors demonstrated that higher RT doses (≥ 75 Gy EQD2) allowed to obtain better outcomes (DSS) irrespective of stage disease: the use of BRA was essential to deliver such high doses to the tumour. At multivariate analysis only the combined-treatment modality "EBRT+BRA" seems to influence significantly the DSS, while the effect of higher total cumulative doses (≥ 75 Gy) do not maintain statistical significance, very likely because of the confounding effect derived from the concentration of all the cases treated with higher EQD2 among those treated with "EBRT+BRA". Furthermore, the OS curves of pts treated with less than 75 Gy EQD2 (+/- CHT) roughly overlaps that of DSS: this suggests that per-

haps other factors could contribute to a worse outcome (e.g. deterioration of performance status justifying the choice of a less aggressive treatment). As already known from the literature data [10-14], in this series LDR BRA and HDR BRA demonstrated the same efficacy; however, in the authors' experience, the use of a BRA boost (especially when delivered with HDR), was associated with a higher number of severe rectal-enteric chronic sequelae and a significant percentage of vaginal stenosis and substenosis. Also G3-G4 rectal-enteric toxicity was found to be correlated to RT-doses (≥ 75 Gy EQD2). Since high radiation-doses are indispensable to obtain tumour regression [18], adjacent organs at risk may receive high doses, thus increasing the probability that severe late toxicity will occur. The authors found an higher number of severe urinary and rectal-enteric late sequelae in pts treated before 2000 as opposed to those treated more recently; however, the incidence of G1/G2 toxicities (involving mostly the rectum and the vagina) that, though mild, can worsen pts quality of life remains a problem also in the more recent years. This mono-institutional analysis, in accordance with the literature [1-9, 19-24], confirms the efficacy of exclusive radical radio-chemotherapy for cervical cancer and underscores the important role of BRA boost both for early stages and for the locally advanced ones, to improve local control and survival. Since women affected by cervical cancer have a reasonably good prognosis, the reduction of late toxicity is an important endpoint to achieve to offer them a better quality of life: the percentage of serious chronic sequelae should be further reduced by new EBRT techniques (such as pelvic IMRT) and new BRA planning procedures. [25-27] The possible benefits deriving from the adoption of these technical improvements should be validated against the benchmark data obtained from the analysis of large retrospective series like the present one.

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Address reprint requests to:
L. BANDERA, M.D.
Via Monte Grappa, 17
25128 Brescia
e-mail: laurabandera81@gmail.com