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Cervical cancer patterns of care in Italy: A radiation oncology survey of MITO and AIRO GYN groups

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ABSTRACT

Large heterogeneity in therapeutic approaches to cervical cancer (CC) patients has been registered worldwide; a national survey exploring practice settings and equipments in CC treatment was distributed to radiation oncologists. Questionnaires were compiled in 90 of 194 Centers (compliance: 46.3 %). Most of respondents reported the presence of multidisciplinary tumor board, and modern equipments/techniques; 55.5 % of centers reported > 1 brachytherapy (BT) equipment, thus implying the need to refer their patients outside for the remaining centers. Post-surgery radiotherapy was performed in 96.7 % of early CC (ECC) cases with pathological high risk factors. Exclusive chemoradiation with concomitant platinum schedules was referred to be used by 84.4 % of centers in locally advanced CC. Alternative options were reported with a range between 4.4 and 28.9 %.

The present survey reports a broad spectrum of therapeutic options for CC in Italy. Availability and use of modern techniques is quite diffuse, but the distribution of BT resources and skills remains a challenge.

1. Introduction

According to the latest GLOBOCAN data, incidence of cervical cancer (CC) in 2018 was reported to range between 6.4–6.8 new cases/100,000 women/year in Northern America and Western Europe compared to 15.2 and 43.1 new cases/100,000 women/year in South America and South Africa, highlighting the relevant disparities disfavoring low/middle income countries, worldwide (Bray et al., 2018; Randall and Ghebre, 2016). The introduction of Human Papilloma Virus vaccines and implementation of screening procedures have reduced, and still will, the incidence of this tumor in the most developed countries (WHO, 2018); moreover, the World Health Organization has launched a call for action for elimination of cervical cancer through a global strategy with clear goals and targets for the scale-up of Human Papilloma Virus vaccination and cervical screening, particularly in low/middle income countries, for the period 2020–2030 (Canfell, 2020). Until then, mortality due to CC in low/middle income countries represents a dramatic issue, since it is currently 18 times higher than the one observed in developed countries, accounting for up to 90 % of deaths due to CC, worldwide (World Health Organization, 2019).

In Italy, approximately 2100 new cases were reported in 2018 confirming the slow, but progressive decrease in incidence -1.4 %/year) (AIOM Linee guida, 2018); moreover, mortality has been steadily decreasing in the last 20 years, leading to an increased rate of 5-year survival since diagnosis from 63 % to 71 % (AIOM Linee guida, 2018). However, a not negligible heterogeneity of treatments options in CC clinical settings was documented, even in high income countries (Lindsay et al., 2012; Fuglsang et al., 2018; Marnitz et al., 2014; De

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Boer et al., 2017; Basta et al., 2019; Ma et al., 2019; Shahid et al., 2018; Toita et al., 2018), despite the World Health Organization has encouraged to adopt treatments based on high level of evidence, together with adequate number and type of facilities, and multidisciplinary evaluation and management (World Health Organization, 2014).

Based on the 2014 International Federation of Obstetrics and Gynaecology (FIGO) stage (FIGO Committee on Gynecologic Oncology, 2014), the standard of care in early-stage carcinoma (*ECC*: IB1, IIA1), is represented by radical hysterectomy (RH) and pelvic lymphadenectomy, often requiring exclusive post-operative radiotherapy (RT), including external beam radiotherapy (EBRT) ± brachytherapy (BT) in case of intermediate pathologically assessed risk factors known as *Sedlis* criteria (i.e. lymphovascular space invasion, depth of stromal invasion, tumor size), or adjuvant chemoradiotherapy (CRT) in case of high risk factors (Sedlis et al., 1999; Rotman et al., 2006; Peters et al., 2000); nonetheless, in patients with older age, and/or severe morbidities, or just refusing surgery, EBRT or exclusive chemoradiation (eCRT i.e. CRT + BT) could be valid alternatives (Landoni et al., 1997, 2017).

In locally advanced setting (*LACC*: IB2, and IIA2-IVA FIGO stage) the standard treatment was established on the basis of meta-analysis and phase III randomized studies (i.e. prospective, randomized, controlled trials on large patient groups aimed at being the definitive assessment of how effective the treatment is, in comparison with the current 'gold standard' treatment) (Vale et al., 2008; Shrivastava et al., 2018) and consists in eCRT with concurrent cisplatin as single agent (or carboplatin in case of cisplatin intolerance) or cisplatin plus 5-fluorouracil *(NCCN Guidelines version 4, 2019)*.

For the metastatic setting, medical treatment with platinum based-regimens ± bevacizumab represents the standard (Monk et al., 2009; Tewari et al., 2017); on the other hand, the management of oligometastatic/persistent disease, or disease relapse is more complex considering patient features, together with previous treatments (*NCCN Guidelines version 4, 2019*).

The national guidelines shared by the majority of European countries are not so different from the European Society for Medical Oncology, European Society for Radiotherapy & Oncology, and European Society of Gynaecological Oncology guidelines; however, most of the surveys about the patterns of care and retrospective analysis of individual data in this disease reveal deviations in the real practice management (Fuglsang et al., 2018; Marnitz et al., 2014; De Boer et al., 2017; Basta et al., 2019). Our perception in the daily practice as well as at scientific events is that some heterogeneity in the therapeutic approach to different clinical settings in this neoplasia are also present in our Country; however, the vast majority of Italian surveys on CC are predominantly focused on surgical issues or preventive procedures (Ciavattini et al., 2017; Zucchetto et al., 2013), while concerning radiotherapy, the only available data are limited to BT, also defined "interventional radiotherapy" (Autorino et al., 2018; Tagliaferri et al., 2017). In this context, the Multicenter Italian Trials in Ovarian cancer (MITO group), and the Gynecological group of Italian Association of Radiation Oncology (AIRO-Gyn) have planned to set up a national survey investigating the current patterns of care for every clinical setting in CC patients.

This survey could provide interesting data relative to the eventual disparity of CC care across our Country, helping to identify possible causes of variations from guidelines, and set up more effective educational efforts to allow for optimization of treatments, and ultimately improve patient care.

2. Materials and methods

The "Patterns of Care in cervical cancer" survey was carried out developing a questionnaire collecting data on routine clinical practice in the management of CC patients among Radiation Oncology centers. A structured questionnaire was designed in collaboration with a panel of radiation oncologists, gynecologist oncologists and data managers; details about type of center/institution, number and features of CC patients treated annually, and type of data archive used, were collected. Readability, usability, and clarity of questions was tested internally by a subset of physicians not directly involved in the survey development, who were also asked to describe drawbacks and provide suggestions for amelioration of the survey itself. The final survey contained 58 questions grouped in 7 sections that investigated demographic aspects, practice settings and equipment (Table 1). The survey was sent out to radiation oncologists working in community hospitals, and academic institutions by an AIRO website facility, an internet program and hosting site that enables investigators to develop a survey for online use (www.surveymonkey.com); the structure and format allowed the direct capture of data into an *excel* database amenable to be subsequently used for statistical analysis. Authors and respondents declared no conflict of interest and no financial support. The online questionnaire was open for completion between July and September 2018.

Table 1
Questionnaire sections.

Section 1 **(Q1–10): background information**
Logistical-structural data as geographic site, address; affiliation; methodology of work; main facilities and technique routinely used in CC treatment.
Section2(Q11–15): radiotherapy assessment
CC patients treated per year according to stage
Section3(Q16–30): staging exams and CC treatment according to stage
Staging procedure in early and LACC patients (multiple choices); treatment's type
Section 4 **(Q31–35): focus on postoperative treatment of early stage CC**
Postoperative radiotherapy setting: doses, techniques and concomitant drugs schedules
Section 5 (Q36–42): focus on treatment choice in the metastatic or recurrent CC
Metastatic or recurrent CC setting: doses, techniques and concomitant drugs schedules
Section 6 (Q43–51): radiotherapy set up and delivery procedures
Technical external beam radiotherapy details
Section 7 (Q52–58): brachytherapy
Brachytherapy details

Q: questions; CC: cervical cancer.

2.1. Statistical analysis

The data processing was performed at Fondazione IRCCS Istituto Nazionale Tumori, Milan in collaboration with Gemelli Molise Hospital, and Fondazione Policlinico Universitario A. Gemelli, IRCCS, Universita' Cattolica del Sacro Cuore, Rome in the first months of 2019. Frequencies and/or percentages were used to present data distribution. Descriptive statistics were utilized to analyze features of centers/institutions participating to the survey as well as distribution of responses according to subgroups. Percentages are always related to the number of responders to the respective questions. All analyses were performed by SPSS statistical software, version 20 (SPSS Inc., Chicago, IL, USA).

3. Results

Ninety questionnaires, accounting for 46.3 % of the 194 Italian radiotherapy centers were returned and collected on the AIRO website; the responding centers were representative of all regions, reflecting the distribution of RT centers throughout the Country (Supplementary Fig. 1). As summarised in Table 2, 37 centers (41.1 %) were located in Northern Italy, and the remaining 30 (33.3 %), and 23 (25.5 %) were distributed between the Centre and South of Italy.

Participants practiced at national community hospitals (N = 55, 61.1 %), academic institutions (N = 19, 21.1 %), and other settings (private clinics, etc) (N = 16, 17.8 %). The vast majority of respondents (N = 73, 81.1 %) were part of one or more scientific societies/cooperative groups, and 15 (16.7 %) declared to routinely enroll patients in clinical trials.

Patient data collection was carried out by electronic archive (N =

Table 2
Geographic areas and practice settings.

	N. Centers/Institutions (%)[a]
Geographic area	
North	37 (41.1)
Center	30 (33.3)
South	23 (25.5)
Practice Setting	
Community Hospitals	55 (61.1)
Academic Institutions	19 (21.1)
Private centers	16 (17.8)
Scientific societies/Cooperative groups membership	
No	17 (18.9)
Yes	73 (81.1)
Data archive system	
Electronic archive	27 (30.0)
Hard copy archive	7 (7.8)
Both	56 (62.2)
Multidisciplinary Tumor Board	
No	11 (12.2)
Yes	79 (87.8)
Scheduled meetings	71 (89.9)
Upon request	8 (10.1)

[a] Calculated on responding Centers.

27, 30.0 %), with a large group of participants (N = 56, 62.2 %) declaring to use both hard copy and electronic archive.

The presence of a dedicated CC multidisciplinary tumor board was reported in 87.8 % of responding centers; gynecologic oncologists and radiation oncologists were always represented, while medical oncologists, pathologists and radiologists were represented in 86.0 %, 65.8 % and 63.2 % of responding centers, respectively (data not shown). Nuclear medicine physicians and psychologists were less frequently represented (25.3 % and 15.1 %, respectively). Members of the multidisciplinary tumor board regularly in 89.8 % of responding centers; the meeting was scheduled upon request in the remaining centers.

Table 3 reports details relative to technical facilities and equipments utilized for cervical cancer radiotherapy. At the time of survey, 75 (83.3 %) of the Centers had at least one linear accelerator combined with an image guided radiotherapy system (IGRT-LINAC). The most frequently used radiotherapy techniques were volumetric arc (VMAT, 67.8 %), and intensity-modulated techniques (IMRT, 48.9 %). Concerning brachytherapy, 50 centers (55.5 %) reported the presence of $\geq$1 radioactive source projectors, while the remaining centers referred their patients elsewhere for BT (data not shown).

Radiotherapy boost on high-risk volumes (i.e. positive lymph nodes and/or margins and/or parametrial spread, and/or tumor size > 4 cm and/or lymph vascular space invasion and/or deep stromal invasion) was given using stereotactic body irradiation instead of BT in a minority of cases (N = 8, 8.9 %), while BT was the most frequent technique to deliver extra-dose (data not shown). In detail, high-dose rate (HDR) BT units were available in 48 centers, with a wide range of treated patients per year (1–80) according to expertise and facilities. Pulsed-dose rate (PDR) units and low-dose rate (LDR) afterloaders were reported by 7 and 3 centers, respectively.

For sake of clarity, additional technical aspects are summarized in Table 3.

3.1. Patients and staging

The number of patients per year was variable: 37 centers (41.1 %) referred to treat $\leq$10 CC/year, 39 centers (43.3 %) reported to treat 11–30 CC/year, and 14 centers (15.5 %) declared to manage > 30 CC patients/year (Table 4). Around two thirds of centers (N = 58, 64.4 %)

Table 3
Facilities, equipments and radiotherapy techniques.

	N. Centers/Institutions (%)
EBRT Equipment[a]	
LINAC with IGRT system	75 (83.3)
LINAC without IGRT system	34 (37.7)
Tomotherapy	19 (21.1)
Cyberknife	4 (4.4)
EBRT techniques[a]	
VMAT	61 (67.8)
IMRT	44 (48.9)
3D-CRT	33 (36.6)
BT Equipment and techniques[a]	
No	40 (44.5)
Yes	50 (55.5)
HDR	*48 (53.3)*
PDR	*7 (7.8)*
LDR	*3 (3.3)*
Simulation Equipment[a]	
CT-Simulator	65 (72.2)
4D-CT-Simulator	32 (35.5)
Simulator	8 (8.9)
External beam radiotherapy technical details	
Set-up immobilization systems	
No	14 (15.5)
Yes	76 (84.4)
Bladder filling	
No	12 (13.3)
Yes	78 (86.7)
Rectal filling	
No	30 (33.3)
Yes	60 (66.7)
Contrast media at simulation	
No	70 (77.8)
Yes	20 (22.2)
oral	*6 (6.7)*
intravenous	*12 (13.3)*
both	*2 (2.2)*
Delineation on CT–MRI	
No	16 (17.8)
Yes	74 (82.2)
Delineation on CT-PET	
No	11 (12.2)
Yes	79 (87.8)
Interfractions checks	
No	6 (6.7)
Yes	84 (93.3)
Intrafraction checks	
No	48 (53.3)
Yes	42 (46.7)
Brachytherapy technical details	
3D treatment planning	
Yes	46 (51.1)
n.a.	44
Imaging for planning	
CT scan	46 (51.1)
MRI	12
Plan per each fraction	
No	11 (12.2)
Yes	35 (38.9)
n.a.	*44*
Pain control procedures	

(*continued on next page*)

Table 3 (*continued*)

	N. Centers/Institutions (%)
Analgesics administered by Radiation Oncologist	24 (26.7)
Analgesics administered by Anaesthesiologist	17 (18.9)
No analgesia,	5 (5.5)
n.a.	*44*

EBRT: external beam radiotherapy, BT: brachytherapy, VMAT: volumetric arc radiotherapy, IMRT: intensity-modulated radiotherapy, *n.a.*: not available.
[a] Multiple choices.

Table 4
Cervical cancer figures according to stage.

	N. Centers/Institutions (%)
CC patients treated at Your Institution within the last year	
$\leq$10	37 (41.1)
11–30	39 (43.3)
> 30	14 (15.5)
ECC distribution (%)[a]	
0–25	58 (64.4)
25–50	27 (30.0)
50–75	5 (5.5)
75–100	0 (0.0)
LACC distribution (%)[a]	
0–25	3 (3.3)
25–50	26 (28.9)
50–75	25 (27.8)
75–100	36 (40.0)
IVB distribution (%)[a]	
0–25	84 (93.3)
25–50	5 (5.5)
50–75	1 (1.1)
75–100	0 (0.0)

[a] Percentage of ECC, or LACC, or FIGO stage IVB among the overall cervical cancer patients/year.

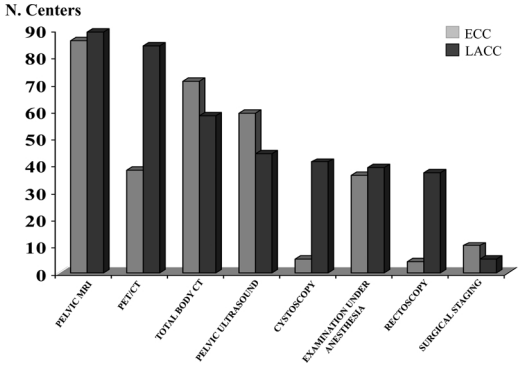

Fig. 1. Staging procedures in ECC and LACC patients.

referred to manage ECC patients in a percentage up to 25 %; conversely, 58 centers (64.4 %) reported to treat $\geq$50 % of LACC patients. The vast majority of centers (N = 84, 93.3 %) managed stage IVB disease in a proportion of $\leq$25 % in their overall CC patients/year. Fig. 1 depicts staging procedures in ECC and LACC patients; in particular, magnetic resonance imaging (MRI) was performed in > 95 % centers in ECC as well as in LACC settings, while positron emission tomography combined with computed tomography (PET-CT) scan was mostly performed in LACC patients (93.3 %), while total body computed tomography (CT) was more frequently adopted in ECC (78.8 %). Examination under anesthesia was performed in 40.0 %, and 43.3 % of centers in ECC and LACC, respectively.

3.2. Treatment of ECC

As far as the post-surgery treatment is concerned, the vast majority of centers (N = 87, 96.7 %) declared to follow the guideline recommendations based on high risk factors as pathologically assessed (Peters et al., 2000; Landoni et al., 1997, 2017); as summarized in Table 5, median total dose was 50 Gy (range: 45–66) with concomitant chemotherapy being most frequently represented by cisplatin weekly. Twenty-eight centers declared to prescribe additional BT (median dose:10 Gy, range 5–30) with HDR in 27 centers. In case of ECC endowed with intermediate risk factors (Sedlis et al., 1999; Rotman et al., 2006), adjuvant EBRT $\pm$ BT was the most frequent choice (N56, 62.2 %), while CRT $\pm$ BT was adopted by 34 (37.8 %) centers (Table 5).

3.3. Treatment of LACC

As shown in Table 6, the preferred treatment in the LACC setting was represented by eCRT in 76 (84.4 %) of centers, with concomitant chemotherapy mostly represented by platinum-based regimen (CDDP 40 mg/m^2 once a week for 5–6 weeks). Notably, only 47 (61.8 %) centers used image guided radiotherapy for treatment monitoring (data not shown). The median EBRT total dose was 50 Gy at conventional fractionation (range: 45 − 72 Gy). Thirty respondents boosted on pathologic lymph nodes (range of dose: 10 − 20 Gy), and 24 respondents used the simultaneous integrated boost technique (data not shown). Brachytherapy boost on high risk volumes was performed indoor in 42 Centers at the median dose of 28 Gy (HDR), or 25 − 30 Gy/0.5-0.6 Gy/h (PDR); 34 centers declared refer patients to other Institutions. Among the other therapeutic approaches, neoadjuvant chemotherapy (NACT) followed by eCRT was adopted by nearly one third of respondents (N = 26, 28.9 %); the most frequent CT schedule was Carboplatin-Taxol q21, for 3–6 cycles or weekly schedule (N = 14). Details about eCRT are summarised in Table 6.

CRT followed by radical surgery (RS) instead of BT, was chosen by 13 (14.4 %) centers that used a range of total dose from 39.6–60 Gy (1.8–2.2 Gy/fraction), and concomitant platinum-based schedules. Radical hysterectomy and pelvic $\pm$ aortic lymphadenectomy were performed after 6–8 weeks from completion of chemoradiation.

NACT followed by radical surgery was the treatment of choice in 13 (14.4 %) centers, while NACT plus chemoradiation followed by radical surgery was adopted in 6 Centers (6.7 %).

Finally, eCRT (48.8 Gy/1.8 Gy/fraction) with HDR boost (28 Gy in 4 fractions) followed by chemotherapy (4–6 cycles Carboplatin/Taxol, q21) was reported only by 4 Centers.

3.4. Oligo-metastatic or recurrent setting

Relapse sites observed by radiation oncologists were mainly represented by lymph nodes (48.9 %) or the central pelvis (15.5 %), either recurring after surgery or radiotherapy. Sixty-seven (74.4 %) and 48 (53.3 %) centers declared to have managed $\leq$5 recurrences post-surgery and post-irradiation, respectively (Table 7). In summary, EBRT and stereotactic techniques were used in 57.7 %, and 20.0 % of centers, while BT was limited to 9% of treatment.

Chemotherapy was also frequently offered, mainly represented by Carboplatin-Taxol q21 (53 out of 78 respondents, 67.9 %), or Cisplatin-Taxol q21 (15 out of 78 respondents, 19.2 %) (data not shown).

4. Discussion

To the best of our knowledge, few studies have been published over time relative to the real life management of CC in Europe (Fuglsang et al., 2018; Marnitz et al., 2014; De Boer et al., 2017; Basta et al., 2019); however, no data about the practice patterns of CC treatment have been reported in Italy. In the present paper, we explored the patterns of therapeutic approaches to CC from the perspectives of

Table 5
Treatment of ECC patients after surgery.

	No. (%)	External Beam Radiotherapy Median dose, fraction range (Gy)	Technique[a]	Concomitant CT[a] Drugs, schedule	Brachytherapy Median dose, fraction range (Gy)	Technique[a]
Positive lymph nodes and/or margins and/or parametrial spread (Peters et al., 2000)						
eCRT[a]	87 (96.7)	50 1.8 45–66	VMAT: 65 IMRT: 38 3D: 13 *n.a: 1*	CDDP, w: 63 CBDCA, w: 3 CDDP ± /5FU, q28: 2 CDDP + T: 1 *n.a: 18*	10 5 5-30	HDR: 27 PDR: 1 *n.a: 59*
RT[a]	3 (3.3)	52 2 45–60	VMAT: 2 IMRT: 1	–	10 5 10–21	HDR: 2 *n.a: 1*
Tumor size > 4 cm and/or lymph vascular space invasion and/or deep stromal invasion (Sedlis et al., 1999; Rotman et al., 2006)						
eCRT[a]	34 (37.8)	45 1.8 45-56	VMAT: 15 IMRT: 12 3D: 3 *n.a: 14*	CDDP, w: 22 CBDCA, w: 2 CDDP ± 5FU, q28: 1 CDDP + T: 1 *n.a: 8*	21 7 20–22.5	HDR: 2 PDR: 1 *n.a: 31*
RT[a]	56 (62.2)	47.5 1.8 45–60	VMAT: 23 IMRT: 9 3D: 10 *n.a: 25*	–	10 5 10–21	HDR: 2 *n.a: 54*

eCRT: exclusive chemoradiation (external ± brachytherapy), CT: chemotherapy, VMAT: volumetric arc therapy; IMRT: Intensity Modulated Radiotherapy, 3D: tridimensional conformal radiotherapy, HDR: high dose rate; PDR: pulsed dose rate, CDDP: cisplatin, CBDCA: carboplatin, 5-FU:5-fluorouracil, T: Taxol, w: weekly,. *n.a.:* not available.
[a] Multiple choices.

Table 6
Treatment of LACC patients.

	No. (%)	Chemotherapy Drugs N. cycles schedule	External Beam Radiotherapy Median dose, fraction range (Gy)	Technique[a]	Concomitant CT[a] Drugs, timing	Brachytherapy Median dose, fraction, range (Gy)	Technique[a]
eCRT[a]	76 (84.4)	–	50 1.8 45–72	VMAT: 57 IMRT: 37 3D: 8	CDDP, w: 67 CBDCA, w: 1 CDDP ± 5FU, q28: 4 CDDP + T: 1 *n.a: 3*	28 7 15-36 25–30 (0.5-0.6 Gy/h)	HDR: 40 PDR: 2 *n.a: 34*
NACT + eCRT[a]	26 (28.9)	CBDCA/T, 3–6, q21 or w:14 CDDP/T/I, 3–6, q21 or w: 8 CDDP/T, 3–6, w: 4	50 1.8 45–66	VMAT: 20 IMRT: 8 3D: 3 *n.a: 1*	CDDP, w: 24 CBDCA, w: 1 *n.a: 1*	28 7 21-30 25–30 (0.5-0.6 Gy/h)	HDR: 13 PDR: 2 *n.a: 11*
NACT + RS[a] *	13 (14.4)	CBDCA/T, 3–6, q21 or w: 9 CDDP/T/I, 3, q21: 3 CDDP/T, 3–6, w:1	– 48.8	– VMAT: 3	– CDDP, w: 4	– 28	–
eCRT + CT	4 (4.4)	CBDCA-T, 3–6, q21 or w: 3 CDDP, w: 1	1.8 45-52.5	*n.a: 1*		7 24-28	HDR: 4
CRT + RS[a] *	13 (14.4)	–	46.3 1.8 39.4-60	VMAT: 8 IMRT: 8 3D: 3	CDDP, w: 11 CDDP ± 5FU, q28: 2	–	–
NAD-CT + CRT + RS[a] *	6 (6.6)	CBDCA-T, 3–6, q21 or w:4 CDDP -T-I, 3, q21: 2	49.9 1.8 40-50.5	VMAT: 4 IMRT: 3	CDDP, w: 4 *n.a: 2*	–	–

eCRT: exclusive chemoradiation (external + brachytherapy), CRT: chemoradiation (external without brachytherapy), NACT: neoadjuvant chemotherapy, RS: radical surgery, VMAT: volumetric arc therapy; IMRT: Intensity Modulated Radiotherapy, 3D: tridimensional conformal radiotherapy HDR: high dose rate, PDR: pulsed dose rate, CDDP: cisplatin, CBDCA: carboplatin, 5-FU:5-fluorouracil, T: Taxol, I: Ifosfamide, q21 each 21 days, w: weekly; q28: each 28 days, *n.a*: not available.
[a] Multiple choices.

Table 7
Patterns of disease relapse and managements.

	N. Centers/Institutions (%)
Recurrences post surgery	
0	6 (6.6)
≤5	61 (67.8)
6–20	9 (10.0)
n.a.	13 (14.4)
Recurrences post RT	
0	12 (13.3)
≤5	36 (40.0)
6–20	6 (6.6)
n.a.	36 (40.0)
Type of recurrences	
Lymph node	44 (48.9)
Central pelvic	14 (15.5)
Mixed (lymph node nd central pelvic)	11 (12.2)
Distant	6 (6.6)
n.a.	15 (16.6)
RT techniques	
EBRT	52 (57.7)
SBRT	18 (20.0)
BT	9 (10.0)
Chemotherapy (Drugs, N. cycles, schedules)	
CBDCA–T, 3–6, q21	53 (67.9)[a]
CDDP-T, 3–6, q21	15 (19.2)[a]

RT: radiotherapy; EBRT: external beam radiotherapy; SBRT: stereotactic body radiotherapy; BT: brachytherapy; CDDP: cisplatin; CBDCA: carboplatin; T: Taxol.
[a] 78 respondents.

radiation oncologists in our Country. It has to be acknowledged that this survey was designed in order to focus the analysis specifically on treatment approaches; therefore, it could have been not entirely comprehensive of some important parameters, such as timing of the diagnostic work-up.

The rate of centers attending the survey was 46.3 %, a figure rather in line with other radiation oncologist surveys (Lindsay et al., 2012; Marnitz et al., 2014; De Boer et al., 2017; Ma et al., 2019; Toita et al., 2018); the absolute number of Radiation Oncologists completing the questionnaire (N = 90) seems to be sufficiently robust and representative of the Italian reality, but the potential weakness of the data originated by the relatively low compliance has to be recognized.

Concerning staging procedures, it has to be considered that gynecologic examination under anesthesia was reported in around 40 % of our respondents, a figure which appears much lower than that reported in other countries (Fuglsang et al., 2018); on the other hand, almost all centers in the current study reported a satisfying agreement with the more complex radiologic staging procedures, even if they are not addressed in the FIGO system, as also acknowledged by a more recent survey (Fuglsang et al., 2018). Although it was not possible to identify the distribution of patterns of the prescribed exams due to the multiple choices allowed in the questionnaire, some considerations can be drawn: for instance, while CT scan was the most frequently reported examination in ECC, the vast majority of respondents declared to routinely adopt PET-CT for LACC pretreatment evaluation (93.3 %), and also for target volume delineation (87.8 %).

The differences with previous surveys are barely ascribed to the professional skills of the first doctor who has seen the patient (i.e. gynecologic oncology surgeons, radiation oncologists, etc), since the CC multidisciplinary tumor board was remarkably reported to be available in 87.8 % of responding centers, with several specialists attending regularly the meetings, and guaranteeing sharing of knowledge and expertise, high quality diagnosis, and evidence-based decision-making. Conversely, it is likely that the different time frames of previous surveys could have had repercussions in terms of underutilization of clinical staging versus an increased use of the imaging approaches over time. Moreover, also the adoption of surgical staging was rarely reported by our respondents (11.1 % for ECC, 5.5 % for LACC) compared to other surveys (Lindsay et al., 2012; Marnitz et al., 2014): this could be related to the fact that, even though a higher rate of upstaging was shown in surgically versus clinically staged LACC patients (33 % versus 8%, p value < 0.001), in face of a slight increased toxicity (Tsunoda et al., 2017, Marnitz et al., 2016), the question of whether surgical staging is beneficial in terms of clinical outcome in the context of primary CRT has been not assessed yet; in this context, the final results of the UTERUS-11 phase III study which aimed at evaluating the role of surgical versus clinical staging in terms of prognosis in chemoradiated FIGO Stage IIB-IVA CC patients are eagerly awaited.

In the postoperative ECC setting, the majority of respondents (96.7 %) declared to prescribe adjuvant CRT in case of high-risk factors; indeed, all guidelines recommend a brachytherapy boost when surgical margins are involved, even though this procedure was not considered in the GOG-109 study (Peters et al., 2000).

Notably, more heterogeneity was reported in terms of treatment options in ECC stage endowed with pathologically assessed intermediate risk factors: indeed, only 62.2 % of respondents reported to adopt external beam radiotherapy, while 34 centers (37.8 %) preferred to adopt chemoradiation; similar uncertainties were also registered in the Germany survey (Marnitz et al., 2014), and can be probably ascribed to the acknowledgement of some pitfalls in the *Sedlis* criteria, such as missing potentially relevant data (i.e. histotype, grade, closed margins and so on) as emphasized in a recent meta-analysis (Li et al., 2019), which seems to demonstrate that CRT would drastically improve progression free survival and overall survival compared to RT alone. In this context, a Phase III randomized study is ongoing investigating adjuvant RT versus CRT in stage I/IIA CC patients with intermediate histological risk factors, i.e. lymphovascular space involvement and/or depth of stromal invasion and/or large tumor diameter) (clinicaltrials.gov, NCT01101451, GOG0263).

Moving to the LACC approaches, the preferred treatment was represented by CRT in nearly 84 % of centers, thus confirming the widespread acceptance of the international guidelines; the median total dose was 50 Gy (range: 45–72), and the concomitant chemotherapy was represented mostly by weekly Cisplatin. The very recent published Phase III randomized trial investigating eCRT versus radiotherapy in stage IIIB squamous CC patients demonstrated a statistically significant superiority of eCRT both in disease free and overall survival, thus providing the first level I evidence in the largest clinical trial reported so far in this poor prognosis setting (Shrivastava et al., 2018). In our survey, NACT followed by eCRT or radical surgery were considered as a possible option in 26 (28.8 %) and 13 (14.4 %) centers, respectively; in particular, the rationale for adopting chemotherapy before eCRT could be explained by the strong motivation to move further, after 20 years of eCRT, trying to implement the current clinical outcome through the control/eradication of micrometastatic disease (McCormack et al., 2013). In this context, the Phase III randomized study (the *Interlace* study, ClinicalTrials.gov Identifier: NCT01566240*)* is investigating the efficacy of 2 cycles of dose dense carboplatin/paclitaxel weekly before eCRT *versus* eCRT only, in LACC patients. Conversely, the choice of NACT followed by radical surgery can be explained on the basis of the strong, long dated medical and surgical tradition in our Country (Benedetti-Panici et al., 2002).

Only 6 centers in our survey declared to prescribe adjuvant chemotherapy after eCRT; indeed, 4 Phase III studies have addressed this issue with conflicting results (Tangjitgamol et al., 2019); an ongoing international randomized trial, the OUTBACK study (ClinicalTrials.gov Identifier: NCT01414608), is investigating the efficacy of eCRT with or without adjuvant chemotherapy in LACC patients.

Finally, 13 centers (14.4 %) declared to carry out CRT followed by radical surgery, and 6 centers (6.6 %) opted for NACT followed by CRT

and radical surgery. Despite the adoption of completion surgery was assessed by several authors (Morice et al., 2012; Cetina et al., 2013; Ferrandina et al., 2010), this approach is often criticized; however, a recently published meta-analysis reported a more favorable progression free survival with adjuvant radical surgery compared to no surgery (Shim et al., 2018). Moreover, even though the available randomized studies did not provide sufficient evidence that surgery could improve overall survival, this is not firmly established, and it has been acknowledged that the adoption of surgery after CRT could be useful in developing countries where there is a limited access to radiotherapy (Kokka et al., 2015).

Furthermore, a comment is needed about the technological implementation of the Italian Radiation Oncology Centers: as per our survey, the modern techniques including on-board imaging and delivery using IMRT/VMAT are largely used, ensuring well tolerated dose delivery, accounting for motion uncertainties, and reducing doses to healthy organs. Indeed, a strict adherence to international guidelines resulted either for external beam either for image guided brachytherapy. A landmark multicentre retrospective study reporting on clinical outcome of a large cohort of patients with LACC who were treated with IGABT (retroEMBRACE) demonstrated an excellent 3-year local and pelvic control rate across all stages with an overall survival benefit of approximately 10 %, and less than 6% G3-4 late toxicities (Sturdza et al., 2016).

One of the major differences with the German survey (Marnitz et al., 2014) was the availability of brachytherapy units among respondents; while in Germany brachytherapy was available for treatment in nearly all departments and institutes (90 %), in Italy only 55.5 % reported the presence of radioactive source projectors, mostly HDR units. Although the technological level can be considered generally high in Italy (Autorino et al., 2018), the lack of widely distributed image guided brachytherapy facilities could influence the choice of treatments other than the standard for a part of CC patients. Moreover, shortage of radiation oncologist staff and substantial more labor and time from multidisciplinary medical team make image guided brachytherapy a complex task, especially nowadays when technological alternatives such as stereotactic radiotherapy and protons try to undermine the supremacy of brachytherapy. Lastly, as in the vast majority of surveys, the data need to be considered as surrogates for the reality of the Country; in fact a quota of radiation oncologists has not responded and therefore the data cannot be considered completely exhaustive.

Therefore, with the limits inherent in the retrospective nature of the survey, these data report a broad spectrum of opinions and clinical pathways in the clinical CC treatment in Italy, that could be overcome with the centralization of care in selected reference centers or with shared national guidelines among the different scientific societies.

Availability and use of modern techniques is quite good, but a more wide distribution of image guided brachytherapy resources and skills still remains a challenge for the future.

In conclusion, this survey has highlighted the gaps in transposing evidence-based strategies as well as consensus guidelines in the real-world management of cervical cancer management; this could be of help in order to focus the attention on specific knowledge and experience grey zones, and plan pertinent educational programs. Furthermore, in this context, an interesting idea could be to collect and analyze the data in a more pan-European perspective with the aim to strengthen the generalizability and universal knowledge value of the data set.

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Declaration of Competing Interest

The authors have declared no conflict of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.critrevonc.2020.102925.

References

AIOM Linee guida, 2018. Neoplasie dell'utero: Endometrio e cervice, p57. www.aiom.it/linee-guida-aiom-2018-nepolasie-utero-endometrio-cervice.

Autorino, R., Vicenzi, L., Tagliaferri, L., Soatti, C., Kovacs, P.G., Aristei, C., 2018. A national survey of AIRO (Italian Association of Radiation Oncology) brachytherapy (Interventional Radiotherapy) study group. J. Contemp. Brachyther. 10 (3), 254–259.

Basta, T., Knapp, P., Blecharz, P., Bodnar, L., Gawron, I., Babczyk, D., Piróg, M., Kluz, T., Markowska, A., Horbaczewska, A., Jach, R., 2019. Current management of cervical cancer in Poland-analysis of the questionnaire trial for the years 2002–2014 in relation to ASCO 2016 recommendations. PLoS One 14 (1), e0209901.

Benedetti-Panici, P., Greggi, S., Colombo, A., Amoroso, M., Smaniotto, D., Giannarelli, D., Amunni, G., Raspagliesi, F., Zola, P., Mangioni, C., Landoni, F., 2002. Neoadjuvant chemotherapy and radical surgery versus exclusive radiotherapy in locally advanced squamous cell cervical cancer: results from the Italian multicenter randomized study. J. Clin. Oncol. 20 (1), 179–188.

Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R.L., Torre, L.A., Jemal, A., 2018. Global cancer statistics 2018: GLOBOCAN estimates of cancer incidence and mortality for 36 cancers in 185 countries. CA Cancer J. Clin. 68, 394–424.

Canfell, K., 2019. Towards the global elimination of cervical cancer. Papillomavirus Res. 100170.

Cetina, L., González-Enciso, A., Cantú, D., Coronel, J., Pérez-Montiel, D., Hinojosa, J., Serrano, A., Rivera, L., Poitevin, A., Mota, A., Trejo, E., Montalvo, G., Muñoz, D., Robles-Flores, J., de la Garza, J., Chanona, J., Jiménez-Lima, R., Wegman, T., Dueñas-González, A., 2013. Brachytherapy versus radical hysterectomy after external beam chemoradiation with gemcitabine plus cisplatin: a randomized, phase III study in IB2-IIB cervical cancer patients. Ann. Oncol. 24 (August (8)), 2043–2047.

Ciavattini, A., Clemente, N., Liverani, C.A., Cattani, P., Giannella, L., Delli Carpini, G., Morini, S., Buttignol, M., Sopracordevole, F., Italian Society of Colposcopy and Cervico-Vaginal Pathology (SICPCV), 2017. Cervical excision procedure: a trend of decreasing length of excision observed in a multicenter survey. J. Low Genit. Tract Dis. 21 (4), 279–283.

De Boer, P., Jürgenliemk-Schulz, I.M., Westerveld, H., de Leeuw, A.A.C., Dávila-Fajardo, R., Rasch, C.R.N., Pieters, B.R., Stalpers, L.J.A., 2017. Patterns of care survey: radiotherapy for women with locally advanced cervical cancer. Radiother. Oncol. 123 (2), 306–311.

Ferrandina, G., Margariti, P.A., Smaniotto, D., Petrillo, M., Salerno, M.G., Fagotti, A., Macchia, G., Morganti, A.G., Cellini, N., Scambia, G., 2010. Long-term analysis of clinical outcome and complications in locally advanced cervical cancer patients administered concomitant chemoradiation followed by radical surgery. Gynecol. Oncol. 119 (3), 404–410.

FIGO Committee on Gynecologic Oncology, 2014. FIGO staging for carcinoma of the vulva, cervix, and corpus uteri. Int. J. Gynaecol. Obstet. 125 (2), 97–98.

Fuglsang, K., Haldorsen, I.S., Avall-Lundqvist, E., Lindahl, G., Roed, H., Woie, K., Pakarinen, P., Thoroddsen, A., Anttila, M., Blaakaer, J., 2018. Cervical cancer staging, pretreatment planning, and surgical treatment in the Nordic countries-Survey from the Surgical Subcommittee of the Nordic Society of Gynecological Oncology. Acta Obstet. Gynecol. Scand. 97 (10), 1178–1184.

Kokka, F., Bryant, A., Brockbank, E., Powell, M., Oram, D., 2015. Hysterectomy with radiotherapy or chemotherapy or both for women with locally advanced cervical cancer. Cochrane Database Syst. Rev. 4, CD010260.

Landoni, F., Maneo, A., Colombo, A., Placa, F., Milani, R., Perego, P., et al., 1997. Randomised study of radical surgery versus radiotherapy for stage IB–IIA cervical cancer. Lancet 350, 535–540.

Landoni, F., Colombo, A., Milani, R., Placa, F., Zanagnolo, V., Mangioni, C., 2017. Randomized study between radical surgery and radiotherapy for the treatment of stage IB–IIA cervical cancer: 20-year update. J. Gynecol. Oncol. 28, e34.

Li, M., Hu, M., Wang, Y., Yang, X., 2019. Adjuvant chemoradiotherapy versus radiotherapy in cervical cancer patients with intermediate-risk factors: a systematic review and meta-analysis. Eur. J. Obstet. Gynecol. Reprod. Biol. 238, 1–6.
Lindsay, R., Paul, J., Siddiqui, N., et al., 2012. Survey on the management of early cervical cancer among members of the GCIG. Int. J. Gynecol. Cancer 22 (9), 1617–1623 2012.
Ma, T.M., Harkenrider, M.M., Yashar, C.M., Viswanathan, A.N., Mayadev, J.S., 2019. Understanding the underutilization of cervical brachytherapy for locally advanced cervical cancer. Brachytherapy 18 (3), 361–369.
Marnitz, S., Köhler, C., Rauer, A., Schneider, A., Budach, V., Tsunoda, A., Mangler, M., 2014. Patterns of care in patients with cervical cancer 2012: results of a survey among German radiotherapy departments and out-patient health care centers. Strahlenther. Onkol. 190 (1), 34–40.
Marnitz, S., Martus, P., Köhler, C., Stromberger, C., Asse, E., Mallmann, P., Schmidberger, H., Affonso Júnior, R.J., Nunes, J.S., Sehouli, J., Budach, V., 2016. Role of surgical versus clinical staging in chemoradiated FIGO Stage IIB-IVA cervical cancer patients-acute toxicity and treatment quality of the Uterus-11 multicenter Phase III intergroup trial of the German Radiation Oncology Group and the Gynecologic Cancer Group. Int. J. Radiat. Oncol. Biol. Phys. 94 (2), 243–253.
McCormack, M., Kadalayil, L., Hackshaw, A., Hall-Craggs, M.A., Symonds, R.P., Warwick, V., Simonds, H., Fernando, I., Hammond, M., James, L., Feeney, A., Ledermann, J.A., 2013. A phase II study of weekly neoadjuvant chemotherapy followed by radical chemoradiation for locally advanced cervical cancer. Br. J. Cancer 108 (12), 2464–2469.
Monk, B.J., Sill, M.W., McMeekin, D.S., Cohn, D.E., Ramondetta, L.M., Boardman, C.H., Benda, J., Cella, D., 2009. Phase III trial of four cisplatin-containing doublet combinations in stage IVB, recurrent, or persistent cervical carcinoma: a Gynecologic Oncology Group study. J. Clin. Oncol. 27 (28), 4649–4655.
Morice, P., Rouanet, P., Rey, A., Romestaing, P., Houvenaeghel, G., Boulanger, J.C., et al., 2012. Results of the GYNECO 02 study, an FNCLCC Phase III trial comparing hysterectomy with no hysterectomy in patients with a (clinical and radiological) complete response after chemoradiation therapy for stage IB or II cervical cancer. Oncologist 17, 64–71.
Peters, W.A., Liu, P.Y., Barrett, R.J., Stock, R.J., Monk, B.J., Berek, J.S., Souhami, L., Grigsby, P., Gordon Jr., W., Alberts, D.S., 2000. Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. J. Clin. Oncol. 18, 1606–1613.
Randall, T.C., Ghebre, R., 2016. Challenges in prevention and care delivery for women with cervical cancer in Sub-Saharan Africa. Front. Oncol. 6, 160.
Rotman, M., Sedlis, A., Piedmonte, M.R., Bundy, B., Lentz, S.S., Muderspach, L.I., Zaino, R.J., 2006. A phase III randomized trial of postoperative pelvic irradiation in Stage IB cervical carcinoma with poor prognostic features: follow-up of a gynecologic oncology group study. Int. J. Radiat. Oncol. Biol. Phys. 65 (1), 169–176.
Sedlis, A., Bundy, B.N., Rotman, M.Z., Lentz, S.S., Muderspach, L.I., Zaino, R.J., 1999. A randomized trial of pelvic radiation therapy versus no further therapy in selected patients with stage IB carcinoma of the cervix after radical hysterectomy and pelvic lymphadenectomy: a Gynecologic Oncology Group Study. Gynecol. Oncol. 73 (2), 177–183.
Shahid, N., Craig, T., Westerland, M., Ashworth, A., Ang, M., D'Souza, D., Sankreacha, R., Fyles, A., Milosevic, M., Kong, I., Cancer Care Ontario Radiation Treatment Gynecologic Oncology Community of Practice, 2018. Moving toward uniform and evidence-based practice of radiotherapy for management of cervical cancer in Ontario, Canada. Brachytherapy 17 (4), 660–666.
Shim, S.H., Kim, S.N., Chae, S.H., Kim, J.E., Lee, S.J., 2018. Impact of adjuvant hysterectomy on prognosis in patients with locally advanced cervical cancer treated with concurrent chemoradiotherapy: a meta-analysis. J. Gynecol. Oncol. 29 (2), e25.
Shrivastava, S., Mahantshetty, U., Engineer, R., Chopra, S., Hawaldar, R., Hande, V., Kerkar, R.A., Maheshwari, A., Shylasree, T.S., Ghosh, J., Bajpai, J., Gurram, L., Gulia, S., Gupta, S., Gynecologic Disease Management Group, 2018. Cisplatin chemoradiotherapy vs radiotherapy in FIGO stage IIIB squamous cell carcinoma of the uterine cervix: a randomized clinical trial. JAMA Oncol. 4 (4), 506–513.
Sturdza, A., Potter, R., Fokdal, L.U., et al., 2016. Image guided brachytherapy in locally advanced cervical cancer: improved pelvic control and survival in Retro- EMBRACE, a multicenter cohort study. Radiother. Oncol. 120, 428–433.
Tagliaferri, L., Kovács, G., Aristei, C., De Sanctis, V., Barbera, F., Morganti, A.G., Casà, C., Pieters, B.R., Russi, E., Livi, L., Corvò, R., Giovagnoni, A., Ricardi, U., Valentini, V., Magrini, S.M., Directors of the Italian Radiation Oncology Schools, 2017. Current state of interventional radiotherapy (brachytherapy) education in Italy: results of the INTERACTS survey. J. Contemp. Brachyther. 11 (1), 48–53.
Tangjitgamol, S., Tharavichitkul, E., Tovanabutra, C., Rongsriyam, K., Asakij, T., Paengchit, K., Sukhaboon, J., Penpattanagul, S., Kridakara, A., Hanprasertpong, J., Chomprasert, K., Wanglikitkoon, S., Atjimakul, T., Pariyawateekul, P., Katanyoo, K., Tanprasert, P., Janweerachai, W., Sangthawan, D., Khunnarong, J., Chottetanaprasith, T., Supawattanabodee, B., Lertsanguansinchai, P., Srisomboon, J., Isaranuwatchai, W., Lorvidhaya, V., 2019. A randomized controlled trial comparing concurrent chemoradiation versus concurrent chemoradiation followed by adjuvant chemotherapy in locally advanced cervical cancer patients: ACTLACC trial. J. Gynecol. Oncol. 30 (4), e82.
Tewari, K.S., Sill, M.W., Penson, R.T., Huang, H., Ramondetta, L.M., Landrum, L.M., Oaknin, A., Reid, T.J., Leitao, M.M., Michael, H.E., DiSaia, P.J., Copeland, L.J., Creasman, W.T., Stehman, F.B., Brady, M.F., Burger, R.A., Thigpen, J.T., Birrer, M.J., Waggoner, S.E., Moore, D.H., Look, K.Y., Koh, W.J., Monk, B.J., 2017. Bevacizumab for advanced cervical cancer: final overall survival and adverse event analysis of a randomised, controlled, open-label, phase 3 trial (Gynecologic Oncology Group 240). Lancet 390 (10103), 1654–1663.
Toita, T., Ohno, T., Ikushima, H., Nishimura, T., Uno, T., Ogawa, K., Onishi, H., Dokiya, T., Itami, J., Working Group of the Japanese Group of Brachytherapy/Japan Society for Radiation Oncology (JGB/JASTRO), 2018. National survey of intracavitary brachytherapy for intact uterine cervical cancer in Japan. J. Radiat. Res. 59 (4), 469–476.
Tsunoda, A.T., Marnitz, S., Soares Nunes, J., Mattos de Cunha Andrade, C.E., Scapulatempo Neto, C., Blohmer, J.U., Herrmann, J., Kerr, L.M., Martus, P., Schneider, A., Favero, G., Köhler, C., 2017. Incidence of histologically proven pelvic and para-aortic lymph node metastases and rate of upstaging in patients with locally advanced cervical cancer: results of a prospective randomized trial. Oncology 92 (4), 213–220.
Vale, C., Tierney, J.F., Stewart, L.A., Brady, M., Dinshaw, K., Jakobsen, A., Parmar, M.K., Thomas, G., Trimble, T., Alberts, D.S., Chen, H., Cikaric, S., Eifel, P.J., Garipagaoglu, M., Keys, H., Kantardzic, N., Lal, P., Lanciano, R., Leborgne, F., Lorvidhaya, V., Onishi, H., Pearcey, R.G., Pras, E., Roberts, K., Rose, P.G., Thomas, G., Whitney, C.W., Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration, 2008. Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: a systematic review and meta-analysis of individual patient data from 18 randomized trials. J. Clin. Oncol. 26 (35), 5802–5812.
WHO, 2018. Cervical Cancer. World Health Organization, Geneva. http://www.who.int/cancer/prevention/diagnosis-screeningcervical-cancer/en.
World Health Organization, 2014. Comprehensive Cervical Cancer Control: A Guide to Essential Practice, 2nd edition. World Health Organization, Geneva, Switzerland.
World Health Organization, 2019. Accelerating the Elimination of Cervical Cancers a Global Public Health Problem. Draft Decision Proposed by Australia, Brazil, Canada, Colombia, Ecuador, India, Kenya, Monaco, Mozambique, New Zealand, Peru, Republic of Korea, South Africa, Sri Lanka, Ukraine, United States of America, Uruguay and the European Union and Its Member States. [Internet] [cited 2019 18 March]. Available from:. World Health Organization, Geneva. http://apps.who.int/gb/ebwha/pdf_files/EB144/B144_CONF1-en.pdf.
Zucchetto, A., Ronco, G., Giorgi Rossi, P., Zappa, M., Ferretti, S., Franzo, A., Falcini, F., Visioli, C.B., Zanetti, R., Biavati, P., La Rosa, F., Baracco, S., Federico, M., Campari, C., De Togni, A., Piffer, S., Pannozzo, F., Fusco, M., Michiara, M., Castaing, M., Seghini, P., Tisano, F., Serraino, D., IMPATTO CERVICE Working Group, 2013. Screening patterns within organized programs and survival of Italian women with invasive cervical cancer. Prev. Med. 57 (3), 220–226.