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Postoperative treatment of intermediate-risk early stage cervical cancer: results of a survey from the Gynecology Study Group in the AIRO Gyn and MITO Groups

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ABSTRACT

This survey investigated prognostic factors, treatment modalities, references followed and radiation oncologists' opinions to prescribe adjuvant therapy in early intermediate-risk cervical cancer. All but one recommended pelvic radiotherapy ± vaginal boost (45%) with or without chemotherapy (20%). 88% believed other prognostic factors could integrate classic risk criteria. 66% considered chemo-radiation indicated in case of lymphovascular invasion and suboptimal node dissection, high grade, size ≥ 4 cm, non squamous histology and risk factors combination. This wide heterogeneity of treatments reflects the different guideline options due to the lack of defined indications. The need of integrating the classic prognostic factors with others factors was unanimously expressed by radiation oncologists. The best local and systemic therapy should be established through new studies. These results highlighted the need of a position paper to standardize adjuvant treatment in Italy and to design collaborative studies to clarify the controversial aspects.

1. Introduction

Cervical carcinoma (CC) is the fourth cause of death in women worldwide, particularly in developing countries. In advanced countries its incidence is declining thanks to HPV vaccination and screening programs (Arbyn et al., 2020). Furthermore, mortality is also decreasing, even in locally advanced disease, thanks to clinical and technological advances and easier access to more appropriate treatments (Arbyn 2020).

Based on the 2014 International Federation of Obstetrics and Gynaecology (FIGO) stage (FIGO Committee on Gynecologic Oncology, 2014), the standard treatment in early-stage CC is represented by radical hysterectomy and pelvic lymphadenectomy; nonetheless, in elderly patients, and/or burdened by severe morbidities, or just refusing surgery, external beam radiotherapy (RT) or exclusive chemoradiation (i.e. concurrent chemotherapy and RT [CCRT]) followed by a brachytherapy

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(BT) boost could be valid alternatives (Landoni et al., 1997, 2017).

In choosing the best initial therapeutic approach for CC patients, radical surgery followed by post-operative RT should be avoided, due to the risk of morbidity which can be linked to the association of these 2 different therapeutic modalities (Tewari and Monk, 2019; Cibula et al. 2018). However, after surgery, depending on whether pathological findings indicate an intermediate or a high risk of recurrence, adjuvant treatments are prescribed (Tewari and Monk, 2019; Cibula et al., 2018). Combinations of "at least 2″ intermediate risk factors (IRF) (i.e: deep stromal invasion, large tumour size ≥ 4 cm and lymph-vascular space involvement [LVI]), commonly known as minor risk factors, constitute the Gynaecologic Oncology Group (GOG) criteria for identifying intermediate-risk patients (Sedlis et al., 1999) for whom adjuvant RT alone is recommended by European guidelines (Cibula et al., 2018) and evidence-based reviews (Tewari and Monk, 2019; Cohen et al., 2019). Indeed, at a median follow-up of 10 years, the results of the randomized study GOG92 (Sedlis et al., 1999; Rotman et al., 2006) showed a significant lower risk of recurrence (HR = 0.54; 90% CI = 0.35–0.81), progression and death (HR = 0.58, 90% CI = 0.40–0.85) in IB patients undergoing adjuvant RT in comparison with those enrolled in the observation arm (Rotman et al., 2006). High grade toxicity rate (6.6% in the RT arm and 2.1% in the observation arm, p = 0.083) and overall survival (OS) (HR = 0.70, 90% CI = 0.45–1.05) were not significantly different between the 2 arms (Rotman et al., 2006). The lack of difference in OS was assumed to be due to the relatively few patients enrolled in the study, the very ambitious statistical hypothesis of a 46% decrease in the hazard rate for OS in the RT arm and the higher percentage of worse prognostic factors in patients enrolled in the RT group (i.e. more adenocarcinomas and more tumours larger than 3 cm) (Rotman et al., 2006).

Conversely, for patients with high-risk factors (i.e. positive lymph nodes, positive margins and parametrial invasion) CCRT represents the standard adjuvant treatment (Tewari and Monk,2019; Cohen et al., 2019). According to recent studies and meta-analyses (Ryu et al., 2011; Sun et al., 2018; Falcetta et al., 2016; Li et al., 2019) CCRT might be more effective than RT alone in improving survival in intermediate risk patients.

When managing intermediate-risk patients in real practice, there are no homogeneous approaches including which type and number of risk factors should be used, BT adoption or not, and even CCRT vs RT alone (Mahmoud et al., 2016; Takekuma et al., 2017). In effect, even when only one IRF is present, including non-squamous cell histology, other national and international guidelines suggested either CCRT or RT alone as adjuvant options (NCCN Guidelines Cervical Cancer, 2019; AIOM Linee guida Neoplasie dell'utero: endometrio e cervice, 2018; Ebina et al., 2019; Beckmann and Mallmann, 2009). In this context, decision-making by Italian radiation oncologists reflected this lack of consensus (Macchia et al., 2020).

Consequently, the Gynecology Study Group of the Italian Association of Radiation and Clinical Oncology (AIRO GYN) along with the Multicenter Italian Trials in Ovarian cancer and gynaecologic malignancies (MITO) group decided to investigate this issue by surveying the risk factors that Italian radiation oncologists take into account in intermediate-risk CC and which schedules of adjuvant treatment they prescribe.

The ultimate objectives were to reach a national agreement on standardising treatment and plan collaborative prospective studies to clarify controversies in adjuvant treatment for early stages disease.

2. Methods

The 21 item questionnaire was designed by the AIRO GYN group steering committee together with a gynaecologic oncologist of MITO executive board to provide insights into current clinical practice in Italy and identify adjuvant treatment indications and modalities in intermediate risk disease. The questionnaire was reviewed and approved by the AIRO Scientific Committee.

Briefly, the questionnaire investigated the type of centre or institution, the specialists' professional experience and views and treatment procedures, with closed and open-ended responses.

Table 1 summarizes the question sections: Section 1 (Q1–4): asked for information about the radiation oncology unit as National Health Service (NHS), university teaching hospital, research centre, private institute etc. and its location in the country, the specialists' professional background and membership of scientific societies.

Section 2 (Q5–8): enquired about the multidisciplinary oncologic group: whether it existed and if so, its composition, decision-sharing procedures, frequency of meetings and number of intermediate-risk patients treated per year.

Section 3 (Q9–13): investigated the specialists' opinions: which guidelines were adopted to prescribe adjuvant therapy, whether integrating common risk criteria (Sedlis et al., 1999) with other factors would improve risk stratification, which factors were taken into account other than GOG criteria (Sedlis et al., 1999), what evidence supported these indications and lastly how many risk factors should be present to prescribe adjuvant treatment.

Section 4 (Q14–21): asked for therapeutic approaches with supporting evidence including which adjuvant therapy to recommend, indications for CCRT, doses and fractionation for RT, BT alone or as a boost and data collection methods.

The AIRO GYN group coordinators invited all 194 heads of Italian radiation oncology centres to participate in the online survey by e-mailing them the cloud-based link (Survey Monkey Europe, UC, Dublin, Ireland). Each centre's senior radiation oncologist with experience in gynaecological oncology was asked to reply. Participation was voluntary without any financial incentives. Ethical Approval was not required.

Replies were processed at the Radiation Oncology Section, University of Perugia and Perugia General Hospital, at the end of 2020. Survey data are presented by descriptive statistics. Response percentages are related to the number of responders to each question.

3. Results

The response rate was 35% as 68/194 Italian radiation oncology centres replied to the questionnaire over a 4-month period from June to September 2020. Response rates ranged from 47% to 100%, according to the question.

3.1. Section 1 (Q1–4): information about the radiation oncology unit and radiation oncologists

Most responses (59/68, 86.8%) came from NHS hospitals, 14 (23.7%) of which were also university teaching hospitals and 9 (15.2%) research centres. Private institutes that were also used by the NHS

Table 1
Questionnaire sections.

Section 1 **(Q1–4): information about the radiation oncology unit and radiation oncologists**: department characteristics (public, private university, etc), geographic area, physician' years of experience, membership in scientific societies.
Section 2 **(Q5–8): multidisciplinary oncologic group:** sharing of decisions making within the Multidisciplinary Gynaecologic Oncology Group, frequency of group meetings, specialists involved, number of intermediate-risk patients treated/year.
Section 3 **(Q9–13): specialists' opinions:** scientific references used in the clinical practice to prescribe adjuvant therapy, usefulness or not of integrating common risk criteria with other factors in order to improve their prognostic role, factors other than GOG criteria considered of prognostic significance, references to support these indication, number of risk factors needed to prescribe adjuvant treatment.
Section 4 **(Q14–21): therapeutic approaches with supporting evidence:** adjuvant therapy prescribed, reference/s supporting this, indication for CCRT, doses and fractionation for external beam RT, BT as administered as unique therapeutic modality or as a boost, type of data collection in each Centre.

Q = questions

accounted for 13.2% (9/68) of responses.

Thirty-four centres (50%) were in Northern Italy, 20 (29.4%) in the Centre and 14 (20.6%) in the South.

Almost all responders were AIRO members (56/68, 82.3%) and 64.2% of them (36/56) were also members of other national or international scientific societies. Over 10 years' experience was reported by 36.8% (25/68) of responders, 13.3% (9/68) reported over 5 years and 7.3% (5/68) under 5 years. Table 2.

3.2. Section 2 (Q5–8): multidisciplinary oncologic group

To record data, 23.5% (16/68), 11.8% (8/68) and 42.6% (29/68) of centres used respectively electronic databases, clinical charts or both. Therapeutic decisions were shared in a multidisciplinary team in 59 centres (86.8%), in weekly (71%) or fortnightly (29%) meetings. In 2 centres (4%) the multidisciplinary meeting was held as required. In 49/59 Centres (83%) the radiation oncologist, gynaecologic oncologist, pathologist and medical oncologist attended the meetings. In 10/59 centres (17%) at least 3 specialists (radiation oncologist, medical oncologist and gynaecologic oncologist) participated in the meetings with or without other specialists.

Each year, 25 centres (36.8%), treated over 10 patients with intermediate risk CC, 22 centres (32.3%) treated 5–10 patients and 21 centres (30.9%) under 5 patients. Table 2.

Table 2
Information about the radiation oncology unit and radiation oncologists, multidisciplinary oncologic group assessment.

	N. Centres/Institutions (%) a
Total responses	68/194 (35)
Geographic area	
North	34 (50)
Center	20 (29.4)
South	14 (20.6)
Practice Setting	
National health service hospitals	59 (86.8)
university hospitals	*14/59 (23.7)*
research centres	*9/59 (15.2)*
Private hospital with public service agreement	9 (13.2)
Years of experience in gynaecological RT	
> 10	25 (36.8)
> 5	9 (13.3)
< 5	5 (7.3)
n.a.	*29*
Scientific societies/Cooperative groups membership	
No	12 (17.7)
Yes	56 (82.3)
Data archive system	
Electronic database	16 (23.5)
Medical records	8 (11.8)
Both	29 (42.6)
n.a.	*15*
Multidisciplinary Tumour Board	
No	9 (13.2)
Yes	59 (86.8)
Weekly	*42/59 (71)*
Every 2 weeks	*15/59 (25)*
Upon request	*2/59 (4)*
Specialists attending the meeting	
all specialists	49/59 (83)
3 specialists	10/59 (17)
Patients treated per year	
>10	25 (36.8)
5–10	22 (32.3)
< 5	21 (30.9)

a Calculated on responding Centres. n.a. = no answer

3.3. Section 3 (Q9–13): the specialists' opinions

Indications to prescribe adjuvant treatment derived from the European Society of Gynaecological Oncology/European Society for Radiotherapy and Oncology/European Society of Pathology European (ESGO-ESTRO-ESP) guidelines (Cibula et al., 2018) for 64.7% (44/68) of responders. GOG Criteria (Sedlis et al., 1999) were followed by 19.1% (13/68) of responders. Other specified reference were followed by 13.2% (9/68) as indicated by the literature (Ryu et al.,2014) or other guidelines (NCCN Guidelines Cervical Cancer, 2019; AIOM Linee guida Neoplasie dell'utero: endometrio e cervice, 2018).

Sixty-six radiation oncologists (97%) replied to the question about the potential integration of GOG criteria (Sedlis et al., 1999) with other risk factors; 6 (8.8%) of them disagreed while 60 (88.2%) were in favour of the integration. The other risk factors included the following: suboptimal surgery for 21/60 (35%) (that was defined by 7 responders as insufficient lymph-node dissection and other 6 provided differing interpretations); histological findings other than squamous cell carcinoma for 19 (31.7%); high grade for 12 (20%); age under 50 years for 3 (5%) and different combinations of these risk factors for 5 (8.3%).

References supporting the consideration of other risk factors were: for 25/60 responders (41.7%) national and/or international guidelines (Cibula et al., 2018; NCCN Guidelines Cervical Cancer, 2019; AIOM Linee guida Neoplasie dell'utero: endometrio e cervice, 2018); a specific study (Ryu et al., 2014) was used by 11 responders (18.3%) while personal experience guided 13 (21.7%). An approach as established by the Radiation Oncology centre was reported by 9 (15%).

As shown in Table 3, for 37 responders (54.4%), 2 or 3 GOG risk factors (Sedlis et al., 1999), i.e. deep stromal invasion, large tumour size $\geq$ 4 cm and LVI, provided the indication for post-operative therapy. For 4 (5.9%), 1 GOG factor + at least two others were needed. For 10 (14.7%), 1 GOG factor + at least one other risk factor were required. Decision-making for 4 (5.9%) was based on 1 GOG factor alone. GOG criteria was not used by 3 (4.4%).

Table 3
Specialists' opinions.

	N. Centres/Institutions (%) a
Referred guideline	
ESGO-ESTRO-ESP [3]	44 (64.7)
GOG criteria [5]	13 (19.1)
Other specified [13,14,18]	9 (13.2)
n.a.	*2*
Prognostic factors integrating GOG criteria [5]	
No	6 (8.8)
Yes	60 (88.2)
Age < 50 yr	*3/60 (5.0)*
Tumor grade	*12/60 (20.0)*
Suboptimal surgery	*21/60 (35.0)*
Non-squamous histology	*19/60 (31.7)*
Multiple factors	*5/60 (8.3)*
n.a.	*2*
References supporting integrating GOG criteria	
Guidelines [3,13,14]	25/60 (41.7)
Clinical trial [18]	11/60 (18.3)
Personal experience	13/60 (21.7)
Centre approach	9/60 (15.0)
n.a.	*2*
Number and type of risk factors for adjuvant RT indication	
At least 2 GOG factors [5]	37 (54.4)
At least 1 GOG factor [5]	4 (5.9)
At least 1 GOG factor [5] and 1 not included	10 (14.7)
At least 1 GOG factor [5] and 2 not included	4 (5.9)
Other risk factors	3 (4.4)
n.a.	*10*

a Calculated on responding Centres. n.a. = no answer. RT = radiotherapy

3.4. Section 4 (Q14-21): therapeutic approaches with supporting evidence

Recommended adjuvant therapy was RT alone for 23 (33.8%), RT and BT boost for 18 (26.5%), CCRT for 8 (11.7%), CCRT and BT boost for 6 (8.8%), BT alone for 1 (1.5%). Choice of adjuvant treatment was supported by current guidelines (35 experts; 31.5%), the institutional approach (15; 22%), reported evidence (5;7.3%) and personal experience (1;1.5%).

CCRT was required in case of multiple or specific risk factors according to 45 radiation oncologists (66.2%). Factors included: positive LVI and suboptimal lymph node dissection for 35 (51.5%), high grade tumour for 23 (33.8%), tumour diameter $\geq$ 4 cm for 20 (29.4%), histology other than squamous cell carcinoma for 20 (29.4%), more than one third stromal invasion for 2 (4.4%) and close margins for 1 (2.2%). Diverse combinations of risk factors were used by 2 (4.4%). In intermediate risk CC patients 9/60 (13.2%) responders stated that CCRT was never adopted.

Conventional fractionation EBRT was used by 47/68 (69.1%) of responders, with 31/47 (66%) prescribing 50 Gy and 16/47 (34%) prescribing 45–46 Gy to the pelvic lymph nodes and vaginal cuff. Moderate hypo-fractionation with simultaneous integrated boost (SIB) for the vaginal cuff and conventional fractionation for pelvic nodes was administered by 7/68 (10.3%). In this case, the total dose ranged from 55 to 60 Gy, with a dose per fraction between 2.2 and 2.4 Gy in 25–28 fractions.

High dose-rate BT was available at the Radiation Oncology centre according to 32 (47.1%) radiation oncologists. Patients were referred to another Radiation Oncology centre by 22 (32.3%). BT boost dose was extremely variable, with the majority of radiation oncologists administering 10 Gy in 2 fractions (14, 43.7%). Table 4 summarized the data relative to operative procedures.

Table 4
Therapeutic approaches with supporting evidence.

	N. Centres/Institutions (%) a
Recommended adjuvant therapy	
External beam RT	23 (33.8)
External beam RT and BT boost	18 (26.5)
CCRT	8 (11.7)
CCRT and BT boost	6 (8.8)
BT alone	1 (1.5)
n.a.	*12*
References supporting the choice	
Current guidelines	35 (51.5)
Institutional approach	15 (22.0)
Evidences from published studies	5 (7.3)
Personal experience	1 (1.5)
n.a.	*12*
Indications for CCRT:	
Never	9 (13.2)
Yes*	45 (66.2)
LVI-ς and suboptimal node dissection	*35/45 (51.5)*
high grade	*23/45 (33.8)*
tumour diameter > 4 cm	*20/45 (29.4)*
other histology	*20/45 (29.4)*
> 1/3 stromal invasion	*2/45 (4.4)*
close margins	*1/45 (2.2)*
multiple risk factors	*2/45 (4.4)*
n.a.	*14*
External beam RT	
Conventional fractionation	47 (69.1)
50 Gy	*31/47 (66.0)*
45–46 Gy	*16/47 (34.0)*
Conventional fractionation + SIB vaginal cuff	7 (10.3)
Other fractionations	1 (1.5)
n.a.	*13*
Vaginal BT boost	
Home High dose-rate BT	32 (47.1)
Another Centre	22 (32.3)
n.a.	*14*
Vaginal BT boost doses §	
10 Gy in 2 fractions	*14/32 (43.8)*
15 Gy in 3 fractions	*6/32 (18.8)*
10–15 Gy in 2–3 fractions	*3/32 (9.4))*
12 Gy in 2 fractions	*2/32 (6.2)*
6 Gy single fraction	*2/32 (6.2))*
21 Gy in 3 fractions	*2/32 (6.2)*
Other fractionations	*3/32 (9.4)*

a Calculated on responding Centres. * multiple choice. ς Lymph-vascular space involvement. SIB = simultaneous integrated boost. CCRT = concurrent chemoradiotherapy. RT= radiotherapy. BT = brachytherapy. § open-ended response

4. Discussion and conclusions

Given the lack of definitive indications (NCCN Guidelines Cervical Cancer, 2019; AIOM Linee guida Neoplasie dell'utero: endometrio e cervice, 2018; Ebina et al., 2019; Beckmann and Mallmann, 2009) and different adjuvant treatments observed in daily clinical practice (Macchia et al., 2020) for intermediate-risk CC, the present survey investigated Italian radiation oncologists' views and the technical aspects of the adjuvant treatments they prescribed. Its strength and novelty lie in their indicating which scientific references were used to prescribe adjuvant treatment and whether considering additional risk factors might improve risk stratification and treatment decision making.

The COVID 19 pandemic may have reduced the number of responses. Even though 35% participation rate by Italian Radiation Oncology centres was similar to what Autorino et al. (2018) reported in their investigation into BT resources and practice patterns in Italy, it was, however, lower than 46% response rate that was achieved by Macchia et al. (2020). Concurring substantially with previous Italian findings on CC (Macchia et al., 2020), all responders were radiation oncologists, who were skilled in gynaecological oncology with most having over 5 years' experience. A large majority were members of AIRO and/or other Scientific Societies. Decision making was shared in multidisciplinary meetings in more than 86% of Radiation Oncology centres.

Like previous surveys in Italy (Macchia et al. 2020) and in other countries (Ikeda et al., 2016; Dostalek et al., 2018; Marnitz et al., 2014), the present investigation demonstrated that adjuvant treatment for intermediate-risk CC is greatly variable in the clinical practice, regarding the type and number of risk factors that were considered and the type of treatment itself (CCRT or RT with or without vaginal boost). Reflecting differences in guideline indications (Takekuma et al., 2017) along with recent evidence of improved outcomes after CCRT (Ryu et al., 2011; Sun et al., 2018; Falcetta et al., 2016; Li et al., 2019) in intermediate-risk CC, controversial features in the IRF group were related to the histological type, the number of risk factors that were required and the use of CCRT instead of RT alone.

Nevertheless, the role of adjuvant CCRT is still controversial in intermediate-risk disease. CCRT, compared with RT alone, was not associated with a survival benefit in 869 patients from National Cancer Data Base (NCDB) report (Mahmoud et al., 2016) and a recent meta-analysis (Sagi-Dain et al., 2019) including a total of 591 patients, found adjuvant RT reduced the risk of recurrence and could have improved survival in patients with 2 IRF.

However, until recently, apart from the GOG 92 (Sedlis et al., 1999; Rotman et al., 2006), other randomized trials were lacking in this setting and so systematic reviews (Falcetta et al., 2016; Li et al., 2019) have analysed data from non-randomized studies. A recently published Chinese study (Huang et al., 2021) compared outcomes after adjuvant RT alone, CCRT and sequential chemotherapy and RT in high- and intermediate-risk patients with positive LVI and deep stromal invasion. Sequential chemotherapy and RT were associated with a better 3-year disease free survival and fewer distant metastases than the other 2 schedules and reduced the risk of cancer specific death compared with RT alone. Despite the study limitations (Randall et al., 2021), these results seem to indicate that chemotherapy should be integrated with RT in intermediate-risk disease. Therefore, as the best schedule of treatment

is not clearly established, results from the ongoing randomized GOG0263 study investigating CCRT versus RT alone in intermediate-risk patients, as defined by the GOG criteria (Sedlis et al., 1999), are awaiting.

Number and type of minor risk factors leading to adjuvant therapy remain a debated issue. However, the need to consider additional prognostic factors along with the GOG criteria has recently been highlighted (Levinson et al., 2021, Kidd et al., 2022). Even though 80% of Italian radiation oncologists adhered to the ESTRO-ESGO-ESP guidelines (Cibula et al., 2018) or the GOG 92 study (Sedlis et al., 1999), which concur on risk classes and adjuvant treatment for intermediate-risk CC, the majority (88%) were of the opinion that other risk factors (LVI and suboptimal surgery, other histology than squamous cell carcinoma, high grade disease, age less than 50 years, close surgical margins and different combination of these factors) should be considered when prescribing adjuvant treatment. When asked how many and which factors to consider, about 20% stated they prescribed adjuvant treatment with pathological findings of just one GOG factor (Sedlis et al., 1999), with or without any other, concurring with evidence from other surveys (Macchia et al., 2020; Ikeda et al., 2016; Dostalek et al., 2018; Marnitz et al., 2014). In fact, 81% of ESGO members considered a combination of GOG adverse prognostic factors (Sedlis et al., 1999) as an indication for adjuvant RT (Dostalek et al., 2018). Moreover, a Japanese survey (Ikeda et al., 2016) reported an extensive use of chemotherapy alone, due in part to reported RT-linked toxicity. On the other hand, in agreement with NCCN indications (NCCN Guidelines Cervical Cancer, 2019), a German survey showed the number of radiation oncologists recommending CCRT varied widely in early stage N0, negative margin CC with one or more intermediate risk factors, including LVI, tumour size $\geq$ 4 cm, adenocarcinoma, age $<$ 40 years, grade 3 disease (Marnitz et al., 2014).

In the present survey the main reasons for performing adjuvant CCRT according to 51% of responders were insufficient lymphadenectomy and LVI, which is a major predictor of lymph node involvement and might be associated with occult micrometastases (Marchiolé et al., 2005). Since both could be evidence of underestimated nodal disease, they support the use of adjuvant CCRT.

When prescribing adjuvant treatment 29% of radiation oncologists considered histology. In effect, given that adenocarcinoma was linked to a worse prognosis than squamous cell carcinoma (Ryu et al., 2014) it was an indication for adjuvant CCRT (NCCN Guidelines Cervical Cancer, 2019; AIOM Linee guida Neoplasie dell'utero: endometrio e cervice, 2018; Ebina et al., 2019), even though histological subtype was not included in the GOG criteria (Sedlis et al., 1999). However, histological subtype emerged as a risk factor for relapse when associated with some GOG IRF (e.g. squamous cell carcinoma with deep stromal invasion and adenocarcinoma with large tumour size and LVI were associated with the highest risk for relapse) (Levinson et al., 2021).

CCRT was suggested in cases of close margins with or without other factors. Even though they are not clearly established as an independent prognostic factor of increased risk of relapse, a margin under 5 mm was linked with increased risk of relapse (McCann et al., 2013). Since "close" margins were often found together with other adverse risk factors, further investigations are needed to determine whether they constitute an IRF (McCann et al., 2013).

Regardless of margin width, more than 35% of radiation oncologists delivered the vaginal cuff BT boost to intermediate risk patients. Another 10% performed vaginal cuff boost through moderate hypofractionation along with standard fractionation on pelvic nodes. Therefore, in clinical practice, a vaginal boost, of generally 10–15 Gy equivalent dose, was delivered through BT or external beam RT, in over 45% of Italian Radiation Oncology centres. Although the role of vaginal boost in patients with close margins was not investigated in randomized trials, some guidelines (NCCN Guidelines Cervical Cancer, 2019; AIOM Linee guida Neoplasie dell'utero: endometrio e cervice, 2018) recommended its use in intermediate-risk patients. Retrospective studies provided conflicting results in patients with intermediate or high risk factors (Gultekin et al., 2021; Lan et al., 2017; Mauro et al., 2019) or more than 8 cm residual vagina. Also, of note, the GOG 109 study (Peters et al., 2000) demonstrated better progression free survival and OS with CCRT rather than RT alone without vaginal boost in high risk patients (including those with positive margins). At present, if a vaginal cuff boost through BT or external beam RT becomes a standard or selected indication in intermediate risk patients requires further evaluation of its efficacy and toxicity. Other than as a boost, BT can be used as a sole treatment. Although adjuvant BT alone is not recommended in intermediate-risk diseases, uterovaginal BT may be an option in the pre-operative setting (Chargari et al., 2022). Indeed, experienced teams have used this approach in early stage CC patients with adverse prognostic factors at diagnosis; a high rate of local control was achieved with low morbidity, thus avoiding the need for postoperative RT (Varela Cagetti et al., 2021; Gauci et al., 2022).

A minority of Italian radiation oncologists considered high grade disease as risk factor (12/60, 20%) requiring CCRT (23/45, 33.8%). Indeed, the effect of grade on prognosis is unclear (AIOM Linee guida Neoplasie dell'utero: endometrio e cervice, 2018; Horn et al., 2019), particularly in squamous cell carcinoma, as a grading system is not universally used by pathologists and results from randomized trials are not yet available.

The effect of patient's age is equally controversial (Brun et al., 2003; Quinn et al., 2019; Ikushima et al., 2007); young patients, according to some Italian radiation oncologists might require CCRT. Interestingly, the NCDB study reported CCRT was generally performed on younger patients with more advanced stage disease (Mahmoud et al., 2016). However, poor outcomes were reported in elderly patients, probably linked to advanced stage disease at diagnosis and less aggressive treatment generally performed (Brun et al., 2003; Quinn et al., 2019) as well as the age itself (Quinn et al., 2019).

In conclusion, present data show that different indications across the guidelines determined the range of diverse options for Italian radiation oncologists in decision making for intermediate-risk patients. Ultimately, the value of each risk factor and of their combinations varies with the knowledge and individual expertise of each physician. Lack of a standard can lead to inadequate treatments and, consequently, suboptimal outcomes. Indeed, undertreatment does not ensure disease control, while overtreatment causes adverse side effects, without providing better outcomes. Therefore, almost all radiation oncologists agreed on the need for more precise risk stratification for adjuvant therapy selection. Standard risk stratification needed to be supplemented by additional factors to identify risk subgroups, as recently evidenced (Kidd et al., 2022). Since new studies are required to optimize local and systemic therapy in different risk groups, the AIRO GYN board, on the basis of the results of the present survey, will write a position paper on adjuvant treatment for intermediate-risk CC patients, and propose collaborative retrospective and prospective studies to clarify controversial areas.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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