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Management of Anal Adenocarcinoma in Italy: National Survey by the Italian Association of Radiotherapy and Clinical Oncology (AIRO) Gastrointestinal Tumors Study Group

Patrizia Pittoni[1]*; Pierfrancesco Franco[2]; Luciana Caravatta[3]; Giuditta Chiloiro[4]; Maria Antonietta Gambacorta[4]; Domenico Genovesi[3]; Marco Lupattelli[5]; Giovanna Mantello[6]; Gianpaolo Montesi[7]; Sabrina Montrone[8]; Francesca Valvo[9]; Luciano Scandolaro[1]

[1]Radiation Oncology Unit, Asst Lariana, Ospedale di Como, 22100 Como, Italy.

[2]Department of Oncology, Radiation Oncology, University of Turin, 10126 Turin, Italy.

[3]Radiation Oncology Unit, 'SS Annunziata Hospital', 'G. D'Annunzio' University of Chieti-Pescara, Via dei Vestini, 66100 Chieti, Italy.

[4]Fondazione Policlinico Universitario 'Agostino Gemelli' IRCCS, Via della Pineta Sacchetti, 00168 Rome, Italy.

[5]Radiation Oncology Section, University of Perugia and Perugia General Hospital, 06156 Perugia, Italy.

[6]Department of Oncology and Radiotherapy, Azienda Ospedaliero Universitaria Ospedali Riuniti, 60002 Ancona, Italy.

[7]Radiation Oncology Department, 'S.M. Della Misericordia' Hospital, AULSS 5 Veneto, Viale Tre Martiri 140, 45100 Rovigo, Italy.

[8]Radiation Oncology Unit, Pisa University Hospital, Via Roma 67, 56123 Pisa, Italy.

[9]Scientific Direction Unit, National Center for Oncological Hadrontherapy (CNAO), Strada Campeggi 53, 27100 Pavia, Italy.

Abstract

Aims: Anal canal adenocarcinoma is a rare neoplasm and there is currently no consensus on optimal management. Indeed, some clinical studies support trimodal therapy (similar to the treatment approach of locally advanced rectal adenocarcinoma) and others studies support definitive radiochemotherapy (similar to anal squamous cell carcinoma). Based on these considerations, a national survey was proposed aimed at evaluating the pattern of care in e anal adenocarcinoma patients in Italy to help standardize future treatment recommendations.

Methods and study design: A questionnaire with 22-item into four-sections was sent to all Italian radiotherapy centers. The four sections aimed t: (1) assess the presence of a multidisciplinary gastro-intestinal tumor board in surveyed hospitals; to describe the exam required in the diagnostic phase; therapeutic approach in adenocarcinoma of the anus; (2) describe simulation details and differences between centers; (3) evaluate the treatment volume identification; (4) describe radiotherapy dose prescription and treatment planning details.

Results: 50 radiotherapy centers joined the survey. Half of the centers treated fewer than 2-5 patients per year. A dedicated multidisciplinary tumor board was reported in 88% of the centers; in particular, radiation oncologists, surgeons and medical oncologists were always represented. The most common examinations

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Correspondance: *Patrizia Pittoni, Radiation Oncology Unit, Asst Lariana, Ospedale di Como, 22100 Como, Italy.*

Email: patrizia.pittoni@asst-lariana.it

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for diagnosis and staging were colonoscopy (100%), lower abdominal magnetic resonance imaging (MRI) (92%), fluorodeoxyglucose positron emission tomography (PET-CT) (86%), abdominal computed tomography (CT) (84%) and chest computed CT (78%). Most participants (68%) consider exclusive radio-chemotherapy as primary treatment, reserving rescue surgery in selected cases where possible (8%); instead, a good part (32%) decides for neoadjuvant radio-chemotherapy followed by surgery (Miles' procedure in the most cases, in a smaller proportion low anterior resection or local excision). The most frequently prescribed dose at the primary (gross tumor volume) GTV ranged from 50 Gy (76%) to 54 Gy (22% - this dose includes boost) for cT1 – T2 disease and 54 Gy (98%) up to 59.4 Gy (28 %) for T3 – T4 disease (total dose including boost). Most participant use intensity modulated and/or volumetric radiotherapy techniques (94%) and employ a simultaneous integrated boost to deliver extra doses to the primary tumor (54%). Concomitant chemotherapy was administred in almost all cases (main schemes were fluoropyrimidines 28% and 5-fluorouracil and mitomycin 31%).

Conclusions: Our survey confirmed a wide variability in the management of adenocarcinoma of anal canal between institutions. This variability can be explained by the diagnostic dilemma between rectal cancer and anal cancer also reported in the literature. This information could help identify targets for future research and investigations.

Introduction

Carcinoma of the anal canal accounts for about 1% of all gastrointestinal cancers. Squamous cell carcinomas constitute the majority, with adenocarcinoma accounting for less than 10% of all anal cancers [1].

Adenocarcinoma of anal canal (AAC) is often thought to be more aggressive than squamous cell carcinomas in term of higher rates of local failure, distant metastasis and disease-associated mortality. Low survival outcomes are also observed in the Franklin et al. and Lewis et al. studies [2,3].

Anal canal adenocarcinomas are defined as tumors with an epicenter located between the anal verge and ≤2 cm above the dentate line. Some anal adenocarcinomas are theorized to originate from the glandular cells of the transitional zone mucosa (colorectal type), whereas others are believed to arise from the anal canal glands (extra mucosal). The latter is more commonly associated with chronic anal fistulas, which, when untreated, may trigger malignant transformation anal gland adenocarcinomas [4].

Studies conducted on anal adenocarcinoma have mostly been smaller retrospective ones and case reports or case series.

Larger retrospective studies Franklin et al and Lewis et al [2,3] and a recent systematic of review of Talidaros [5] provided a more accurate analysis of the management and clinical outcomes of this tumor, showing as adenocarcinoma of the anus reported a more aggressive behavior in comparison to that of the squamous cell type and a worse prognosis than rectal adenocarcinoma. Although the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology, suggest for the management of anal adenocarcinoma neoadjuvant therapy followed by radical surgery with abdominoperineal resection (APR), [6] in clinical practice there is a lack of consensus regarding the optimal management, with some physicians advocating for trimodality therapy (similar to the paradigm employed in locally advanced rectal adenocarcinoma) [7] and others advocating for definitive radiation therapy with concurrent chemotherapy, with abdominoperineal resection (APR) employed for salvage of locally recurrent disease (similar to the management of anal squamous cell carcinoma). In this survey, we describe the approach to the management of this challenging disease in Italian center.

Materials and methods

The project was developed and endorsed by the Italian Association of Radiotherapy Oncology (AIRO) Gastrointestinal Tumors Study Group.

An online survey was carried out using Survey Monkey (www.surveymonkey.com; accessed on September 2020) and was submitted to all the Italian radiotherapy center who have expressed interest in this survey. Only one radiation oncologist per center, expert in gastrointestinal pathology, specifically in the neoplasm of the anus, was allowed to participate in the survey. No personal patients information was collected.

The questionnaire, consisting of 22 items, was organized in four sections (Supplementary Materials).

1. The first section, entitled Taking care and therapeutic approach, was aimed at (1) evaluating the presence of a multidisciplinary gastro-intestinal tumor board in surveyed hospitals; (2) describing the exam required in the diagnostic phase (3) therapeutic approach in adenocarcinoma of the anus.
2. The second section was entitled Patient's Set Up and describe simulation details and differences between centers.
3. The third section, entitled Volume of interest was aimed at evaluating the treatment volume identification.
4. The fourth section, entitled Radiotherapy was aimed at describing radiotherapy dose prescription and treatment.

The Checklist for Reporting Results of Internet E-Surveys (CHERRIES) [8] was followed.

Results

The survey was e-mailed to 60 radiotherapy centers in Italy, and 50 responses were received (response rate 83%).

Section I (Multidisciplinary approach)

Most of the respondents work in public and/or university hospitals (80%). Detailed characteristics of the participants and centers can be found in Table 1. Half centers (50%) treat less than 2-5 patients per year with adenocarcinoma of the anus. The clinical

experience of the participants was almost split between below (60%) and above (40%) 10 years. The presence of a dedicated multidisciplinary tumor board was reported in 88% of responding centers; surgeon, radiotherapist and oncologist were always represented.

Table 1: Detailed characteristics of the participants and centers.

Radiotherapy Facility	N (%)
Public	31 (62%)
Accredited private hospital	6 (12%)
University Hospital	4 (8%)
Accredited cancer center (IRCCS)	9 (18%)
Years of experience in RT	
<10	30 (60%)
>10	20 (40%)
Anal cancer patients treated/year	
<2-5	25 (50%)
5-10	18 (36%)
>10	7 (14%)
MDT dedicated to anal cancer	
Yes	44 (88%)
No	6 (12%)

N: number; IRCCS: Istituto di Ricovero e Cura a carattere scientifico; RT: radiotherapy; MDT: Multidisciplinary Team.

The exams required to stage the disease were in order of higest demand (Table 2) colonoscopy (100%), lower abdomen MRI (92%), PET-CT (86%), abdominal CT (84%) and chest CT (78%).

Table 2: Disease staging (possibility of multiple choice).

Diagnostic test required	N (%)
Colonoscopy	50 (100%)
Lower abdomen MRI	46 (92%)
FDG-PET	43 (86%)
Abdomen CT	42 (84%)
Chest CT	39 (78%)
Ultrasound endoscopy	36 (72%)
Tumor marker (CEA)	35 (70%)
Trans rectal ultrasound	32 (64%)
Upper abdomen MRI	25 (50%)
Abdominal ultrasound	13 (26%)
Chest x-ray	5 (10%)

N: Number; CT: Computed Tomography; MRI: Magnetic Resonance Imaging; FDG-PET: Fluorodeoxyglucose Positron Emission Tomography; CEA: Carcino-Embryonic Antigen.

With regard to the type of treatment chosen in the various centers, most of them (68%) make use of exclusive radio-chemotherapy as primary treatment, reserving salvage surgery for selected cases where possible of uncompleted response; instead, a good part (32%) decides for neoadjuvant radio-chemotherapy followed by surgery (Miles' procedure in the most cases, in a smaller proportion low anterior resection or local excision).

Concomitant chemotherapy was given in almost all cases (the principal schemes were: 28% fluoropyrimidines and 31% 5-fluorouracil and mitomycin).

Section II (Patient's set-up)

Over the last years there have been vast technological developments in the field of external beam radiotherapy, allowing more rigid control over the delivery of radiation fields and providing highly conformal regions of dose. These improvements have led to the requirement of advanced techniques for patient set-up, including on-board imaging devices such as cone-beam computed tomography (CBCT) for image guided radiotherapy. See Table 3 for details.

Table 3: Characteristics of the patient's set up.

Patient's set-up	N (%)
Specific / customized immobilization systems	33 (66%)
Patient's position — Supine — Prone	 46 (92%) 4 (8%)
Anal landmark	33 (66%) of which 13 on specific indication
Bladder filling protocol	36 (72%) of which 4 on specific indication
Contrast agent for simulation CT	12 (24%) of which 8 on specific indication
Fusion diagnostic image — FDG-PET — MRI of lower abdomen	 11 (22%) 6 (12%)

N: Number; CT: Computed Tomography; MRI: Magnetic Resonance Imaging; FDG-PET: Fluorodeoxyglucose Positron Emission Tomography.

Section III (Volume of interest)

The guidelines used by the various centers were the AIRO guidelines referred to the anus district in 66% (RTOG 0529 study) [9] and to the rectum district in 17%; 17% of the centers use other reference guidelines (eg Australian or internal protocols).

The only uniform data is the volume of the high-risk area (tumor and anal canal). A difficulty in defining the areas (high-intermediate and low risk) was identified, most likely due to the heterogeneity of the disease, the therapeutic approach and the technique. This heterogeneity is found for the lymph node areas to be included in the treatment volume, of these areas for example 54% would treat the inguinal station even in the absence of pathological lymph nodes (prophylactic inguinal nodal irradiation).

Section IV (Radiotherapy treatment details)

See Table 4 for details. We investigated total RT dose and daily fractionation prescription in according to clinical stage at presentation, the possibility of delivering an overdose and the techniques applied, in addition to the controls of the set up during radiotherapy treatment.

The most frequently prescribed dose at the primary GTV ranged from 50 Gy (76%) to 54 Gy (22% - this dose includes boost) for cT1 – T2 disease and 54 Gy (98%) up to 59.4 Gy (28 %) for T3 – T4 disease (total dose including boost). Most participant use

intensity modulated and/or volumetric radiotherapy techniques (94%) and employ a simultaneous integrated boost to deliver extra doses to the primary tumor (54%).

Table 4: Radiotherapy treatment details.

Radiotherapy dose prescription and delivery	N (%)
RT delivery technique	
— 3DCRT	3 (6%)
— IMRT	24 (48%)
— VMAT	23 (46%)
Primary tumor boost	
— EBRT-Sequential boost	12 (24%)
— EBRT-SIB	48 (76%)
RT dose to primary tumor GTV for T1–T2 tumors (dose range)	
— 44-.46 Gy	10 (20%)
— 50-50.4 Gy	26 (52%)
— 54-56 Gy	11 (22%)
— 58.8-59.4 Gy	3 (6%)
RT dose to primary tumor GTV for T3–T4 tumors (dose range)	
— 50 Gy	2 (4%)
— 54-55 Gy	15 (30%)
— 56-57.5 Gy	4 (8%)
— 58.8-60 Gy	11 (22%)

N: Number; GTV: Gross Tumor Volume; RT: Radiotherapy; 3DCRT: 3-dimensional conformal radiotherapy; IMRT: Intensity Modulated Radiotherapy; EBRT: External Beam Radiotherapy; SIB: Simultaneous Integrated Boost.

Discussion

In literature the treatment for AAC with the best survival outcomes is neoadjuvant CRT followed by APR (5-year OS, 64.6%), and the worst survival outcomes are in the group treated with CRT alone (5-year OS, 39.2%) [10].

In our survey, on the other hand, it would seem that the treatment of choice is exclusive radiochemotherapy (68%), reserving, where possible, the rescue intervention in selected cases (8%); even if a good part decides instead for neoadjuvant radiochemotherapy and to follow the surgery (32%).

A retrospective analysis of 82 patients with AC of the anus across 11 institutions from the Rare Cancer Network in Europe was performed by Belkacemi and colleagues [11]. The authors analyzed survival in patients treated with primary surgical intervention combined with RT (RT/S group), patients treated with primary CRT, and patients treated with primary APR. The authors found survival benefit for the CRT group in comparison to the other groups. The 5-year OS and 10-year OS were 29% and 23% for the RT/S group, 58% and 39% for the CRT group, and 21% and 21% for APR group. The authors called for combination CRT as the preferred treatment strategy for anal AC for early-stage tumors (≤4 cm) with APR serving as a salvage therapy.

In contrast, several retrospective single-institution studies of AAC have found evidence of improved survival from combining surgical intervention, mainly APR, with adjuvant or neoadjuvant CRT. Beal and colleagues [12] performed a study of 13 patients at Memorial Sloan Kettering Cancer Center and found that patients who were treated with combination APR, with neoadjuvant CRT, or with postoperative CRT had better survival outcomes than patients who underwent local excision with postoperative CRT. Six of 13 patients were disease free after treatment, and, of the 6 patients that were disease free, 5 were treated with APR combined with neoadjuvant or adjuvant CRT. The authors noted that treatment with APR combined with preoperative or postoperative CRT achieves reasonable local disease control and survival benefit for patients with AC of the anus. A study at MD Anderson by Chang et al [13] analyzed survival data of 34 patients with AC of the anus. Of 34 patients, 13 were treated with local tumor excision followed by RT or CRT, and 15 patients underwent radical resection with preoperative or postoperative CRT. The authors found that combined therapy with CRT and radical tumor resection was associated with improved survival outcomes. The median disease-free survival was 13 months for local excision and 32 months after radical surgery. These 2 studies provided evidence of survival benefit for patients with AC of the anus treated with combined modality treatment of radical surgical resection with CRT. Another population-based study was performed by Kounalakis et al, [14] conducted a retrospective analysis of Surveillance, Epidemiology, and End Results data from the years 1988 to 2004 of 196 patients with nonmetastatic AC of the anus and compared the 5-year OS of these patients based on the type of treatment modality that they received. The authors identified 3 treatment groups: patients who were treated with APR only, patients who were treated with APR and external beam radiation (RT/S), and patients who only received external beam radiation treatment. The authors found that patients treated with APR only had the best 5-year OS in this analysis (58% vs 50% for RT/S group vs 30% for external beam radiation only group). The authors concluded that APR with or without external beam radiation therapy was associated with improved survival outcomes for nonmetastatic AC of the anus.

The analysis of Richard Li et al is supportive of national guidelines recommending neoadjuvant CRT followed by resection for patients with locally advanced anal adenocarcinoma. This study showed that CRT followed by surgery was associated with improved survival compared with CRT alone in patients with nonmetastatic adenocarcinoma of the anal canal. However, only 57% of patients receiving CRT subsequently had surgery. [6] Also Taliadoros [5] confirm that trimodality treatment with neoadjuvant chemoradiotherapy followed by radical surgery of abdominoperineal excision of rectum appeared to be the most effective approach.

Study limitations, strengths, and future perspectives

Recent NCCN guidelines sought to standardize anal adenocarcinoma treatment to address the lack of agreed existing practice guidelines and based this on studies such as that of Chang et al. in 2009 and Beal et al. in 2003 [12,13]. In Italy, however, there is still no standard practice on the management of adenocarcinoma of the anus; these limitations also include the fact that anal adenocarcinoma can sometimes be diagnosed incorrectly into its close counterparts such as rectal adenocarcinoma and anal squamous cell carcinoma.

On the basis of the current evidence reported in the literature, it would seem recommended to follow the trimodal therapeutic approach (combination of CRT followed by APER) as it would give better survival results.

More information is needed for a consensus conference aimed at establishing multidisciplinary indications for staging and treat-

ment of adenocarcinoma of the anus.

Declarations

Supplementary materials: Full text questionnaire.

Conflict of interest: The authors declare no conflict of interest

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Supplamentary Files

AIRO – Study group for Gastrointestinal malignancies

Italian investigational survey on the pattern of practice in the multimodal treatment of squamous cell carcinoma of the anus

Anal squamous cell carcinoma is a rare neoplasm, with a growing incidence in Western countries. Evidence from several phase III randomized trials have established definitive radio-chemotherapy as the standard of care. However, some issues related to diagnosis, radiotherapy options in terms of doses, volumes and techniques, as well as systemic therapy, remain controversial. Our Italian survey, proposed by the AIRO study group for Gastrointestinal malignancies, aims to investigate the most common approaches in the management of anal canal cancer patients, in order to find out potential 'gray zones' liable for study initiatives, educational programs, and consensus documents. Your answer to the survey will help us to selectively target research and treatment optimization in this clinical setting. Therefore, we thank you for your contribution.

General profile of the respondent

1) Radiation Oncology Center:

a) Public

b) Private

c) Private in agreement with Public

d) Academic

e) Clinical Academic

f) Research Institute

2) In which Italian Region do you work?

Free text

3) How many years have you been treating squamous anal cancer?

a) < 5 years

b) 5-10 years

c) 11-15 years

d) > 15 years

4) How many patients diagnosed with anal squamous carcinoma are treated annually with radiotherapy in your Radiation Oncology Center?

a) < 10 patients

b) 10-20 patients

c) 21-30 patients

d) > 30 patients

5) Is there a multidisciplinary tumor board for lower gastrointestinal cancers in your center?

a) yes

b) no

Specific questions

6) Which examinations do you use in the initial diagnosis and staging of anal canal cancer (multiple answers allowed)?

a) anoscopy

b) colonoscopy

c) gynecological examination + colposcopy

d) thorax, abdomen and pelvis contrast-enhanced CT

e) contrast-enhanced high resolution pelvic MRI including inguinal region

f) 18FDG-PET CT

g) endo-anal ultrasound

7) How do you consider pelvic MRI as staging exam for squamous anal cancer?

a) a mandatory examination

b) an optional but useful examination

c) a second level examination (in case of clinical doubt)

d) an unnecessary examination

8) How do you consider 18FDG-PET for tumor and nodal staging of squamous carcinoma of the anus?

a) a mandatory examination

b) an optional but useful examination

c) a second level examination (in case of clinical doubt)

d) an unnecessary examination

9) In case of suspected involvement of one (or more) inguinal lymph nodes (diameter > 1 cm), do you suggest a biopsy/ fine needle aspiration?

a) always

b) only in case of a clinically palpable node, suspicious at CT imaging (diameter> 1 cm), with a positive finding at 18FDG-PET

c) in case of a clinically palpable node, suspicious at CT imaging (diameter> 1 cm), with a suspicious 18FDG-PET uptake

d) in case of a clinically palpable node, suspicious at CT imaging (diameter> 1 cm), without an 18FDG-PET uptake

e) never

10) Do you usually request HIV screening on blood and/or saliva?

a) always

b) sometimes

c) only in case of risky behaviors

d) never

11) In your centre, when is HPV screening carried out on biopsy using immunohistochemical examination?

a) always

b) sometimes

c) only in young patients

d) according to investigational protocols

e) never (reason why:....)

12) Which role does the multidisciplinary tumor board play in the staging and treatment approach proposed to patients with squamous cell carcinoma of the anus?

a) standard management for all patients

b) employed only in selected cases

c) not applicable to my routine clinical practice

13) Which imaging modality do you usually prefer, in addition to simulation CT, when defining treatment volumes? (multiple answers allowed)

a) None, I use simulation CT only

b) Contrast-enhanced pelvic CT

c) Contrast-enhanced pelvic MRI

d) 18FDG-PET CT

14) Which radiotherapy technique do you prefer for patients with anal cancer? (multiple answers allowed)

dd) 3DCRT

ee) IMRT

ff) VMAT

gg) Tomotherapy

hh) MRgRT

15) Which external beam radiotherapy (EBRT) technique do you prefer to deliver a boost dose? (multiple answers allowed)

ii) EBRT - sequential boost with photons

jj) EBRT - sequential boost with electrons

kk) EBRT - concomitant or simultaneous integrated boost (SIB)

ll) Endocavitary brachytherapy

mm) Interstitial brachytherapy

nn) Others (specify:…)

16) Which is your typical the prescription dose for elective nodal volumes?

[total dose to positive nodes= …..Gy/[dose/fraction]……Gy/[number of fractions…….]

Comments:….

17) Which is the prescription dose for macroscopically involved nodes?

Node < 3 cm - [total dose to positive nodes= …..Gy/[dose/fraction]……Gy/[number of fractions…….]

Comments:….

Node ≥ 3 cm [total dose to positive nodes= …..Gy/[dose/fraction]……Gy/[number of fractions…….]

Comments:….

18) Which is the prescription dose to primary tumor for stage cT1-T2 disease?

[total dose to primary tumor= …..Gy/[dose/fraction]……Gy/[number of fractions…….]

Comments:….

19) Which is the prescription dose to primary tumor for stage cT3-T4 disease?

[total dose to primary tumor= …..Gy/[dose/fraction]……Gy/[number of fractions…….]

Comments:….

20) In case of unresected cT1N0 anal margin tumor or in case of local excision of anal margin tumor (pT1N0) associated to risk factors at histological examination, what treatment would you consider?

oo) Definitive radiotherapy with curative dose

pp) Radio-chemoterapy with de-escalated radiotherapy (reducing total dose)

qq) Radio-chemoterapy with curative dose

rr) De-escalated radiotherapy (reducing total dose)

ss) Other (specify…)

21) What chemotherapy regimen do you think is the best combined with radiotherapy?

tt) 5-FU-MMC

uu) 5-FU-CDDP

vv) Capecitabine-MMC

ww) Capecitabine-CDDP

xx) Other (specify…)

22) In case of 5-FU/MMC o Cape/MMC chemotherapy regimen, how many MMC cycles do you normally administer to the patient?

yy) One (first RT week)

zz) Two (first and last RT week)

aaa) Other (specify…)

23) Which dose of MMC do you use?

bbb) In case of 1 MMC cycle= ….(mg/m2)

ccc) In case of 2 MMC cycles= ….(mg/m2)

24) Do you usually prescribe a pre-treatment DYPD (Dihydropyrimidine dehydrogenase) polymorphism screening in case of fluoropyrimidine-based chemotherapy regimens?

ddd) Yes

eee) No

25) How do you consider capecitabine in combination with MMC or CDDP concurrent to RT?

fff) Standard of care (for everyday clinical practice)

ggg) Investigational (only in clinical studies)

hhh) Potential option in case of patients' preference or in case of concerns for central venous catheter positioning

iii) Other (specify…)

26) How do you consider CDDP use in addition to 5FU/capecitabine, instead of MMC, combined with RT?

jjj) Equivalent to MMC

kkk) Inferior to MMC

lll) Not the standard of care, but optional in case of clinical contraindication to MMC use (i.e.: predicted hematological toxicity)

mmm) Other (specify…)

27) Do you think induction chemotherapy should be indicated before definitive chemo-radiotherapy for anal cancer?

mmm) Always

nnn) Never

ooo) Only in case of extensive disease (i.e.: lombo-aortic nodal involvement) or extensive pelvic nodal involvement

ppp) Other (specify…)

28) Do you think adjuvant chemotherapy should be indicated after definitive chemo-radiotherapy for anal cancer?

qqq) Ever

rrr) Never

sss) Only in case of high-risk disease (locally advanced tumors with positive nodes) or extensive pelvic nodal involvement

ttt) Other (specify…)

29) Which induction or adjuvant chemotherapy schedule do you use?

induction chemotherapy:……..

adjuvant chemotherapy:……..

30) In your Center, for HIV patients under antiretroviral therapy, which approach do you use for radiochemotherapy?

uuu) Radio-chemotherapy with standard doses and schedules in any case

vvv) Radio-chemotherapy with standard doses and schedules in presence of regular CD4+ count

www) Radio-chemotherapy with standard doses and schedules in presence of regular CD4+ count and HIV RNA undetectable

xxx) Chemotherapy drugs are always reduced in this setting of patients

yyy) Alternative chemotherapy drugs (i.e.: CDDP instead of MMC)

31) Which is the right timing to evaluate response to chemoradiotherapy?

zzz) 8 weeks after the end of RT-CT

aaaa) 3 months after the end of RT-CT

bbbb) 6 months after the end of RT-CT

cccc) >6 months after the end of RT-CT

dddd) 26 weeks after the initiation of RT-CT

32) Which imaging examination do you think is indicated to assess response after RTCT in anal cancer patients? (multiple answers allowed)

eeee) Thorax and abdomen contrast-enhanced CT

ffff) Contrast-enhanced high resolution pelvic MRI including inguinal region

gggg) 18FDG-PET CT

hhhh) Endo-anal ultrasound

33) When do you perform biopsy during evaluation of treatment response?

iiii) Always

jjjj) In case of suspicion for persistent disease or fibrotic residual disease

kkkk) In case of suspicion for persistent disease

llll) Evaluation in terms of tumor response's clearance and type

mmmm) Never

34) In case of persistent or recurrent disease, do you consider salvage surgery as a curative treatment?

nnnn) Yes, always

oooo) Yes, in almost half of the patients

pppp) Never

qqqq) I discuss this therapeutic option during the multidisciplinary board

rrrr) Other (specify…)

35) Which approach do you use to manage recurrent disease?

ssss) Salvage surgery, if possible

tttt) Palliative reirradiation+ chemotherapy

uuuu) Definitive chemotherapy

vvvv) Preoperative reirradiation+ chemotherapy + surgery

36) In your center, in case of metastatic disease, which first line chemotherapy scheme is the standard of care?

zzzz) CDDP-5FU

aaaaa) CBDCA + Paclitaxel

bbbbb) (modified) Docetaxel + CDDP + 5-FU

ccccc) Other (specify…)

37) Which is the management for late toxicity and sequelae in long-survivors?

ddddd) I manage long-term follow-up personally

eeeee) I do not manage long-term follow-up personally

fffff) I rely on other colleagues (surgeon, medical oncologist)

ggggg) I work within the multidisciplinary tumor board

38) Which is the timing of follow-up for anal squamous cell carcinoma?

hhhhh) Every 3 months for 5 years

iiiii) Every 6 months for 5 years

jjjjj) Every 3 months within the first year and every 6 months for the following 4 years

kkkkk) Every 3 months within two years and every 6 months for the following 3 years

lllll) Other (specify…)