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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

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1. Abstract

1.1. 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.

1.2. 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.

1.3. 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 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%).

1.4. 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.

2. 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 (extramucosal). 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 behaviour 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.

3. 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)*.

- 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.
- The second section was entitled *Patient's Set Up*, and describe simulation details and differences between centers.
- The third section, entitled *Volume of interest* was aimed at evaluating the treatment volume identification.
- The forth 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.

4. Results

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

4.1. 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.

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%).

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).

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%)
10-May	18 (36%)
>10	7 (14%)
MDT dedicated to anal cancer	
Yes	44 (88%)
No	6 (12%)

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

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%)

Legend: N: number; CT: computed tomography; MRI: magnetic resonance imaging; FDG-PET: fluorodeoxyglucose positron emission tomography; CEA: carcino-embryonic antigen.

4.2. 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	46 (92%)
- Prone	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	11 (22%)
- MRI of lower abdomen	6 (12%)

Legend: N: number; CT: computed tomography; MRI: magnetic resonance imaging; FDG-PET: fluorodeoxyglucose positron emission tomography.

4.3. 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).

4.4. 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%)

5. 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.

5.1. 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 treatment of adenocarcinoma of the anus.

6. Supplementary Materials

Full text questionnaire.

7. Acknowledgement

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8. Conflicts of Interest

The authors declare no conflict of interest

Anal adenocarcinoma is a rare neoplasm, more aggressive than squamous cell carcinomas. Most of the studies reported in the available in literature were characterized by a small sample size. The NCCN Clinical Practice Guidelines in Oncology recommend a management strategy similar to rectal cancer, consisting of neoadjuvant therapy followed by radical surgery, namely abdominoperineal resection. For patients with localized disease, 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) and others advocating for definitive radiation therapy with concurrent chemotherapy, with abdominoperineal resection employed for salvage of locally recurrent disease (similar to the management of anal squamous cell carcinoma).

Our Italian survey, proposed by the AIRO study group for Gastrointestinal malignancies, aims to investigate the most common approaches in the management of anal adenocarcinoma patients to established consensus for standard of care.

The aim of the project is to provide a vision of current clinical practice, in the Italian reality, in relation to the methods of treating adenocarcinoma of the anus in order to be able, at a later stage, to propose guiding criteria and indications in a multidisciplinary context. Therefore, we thank you for your contribution.

Session 1: CARE AND THERAPEUTIC APPROAC

1. **Radiation Oncology Center:**

   a) Public
   b) Private
   c) Private in agreement with Public
   f) Research Institute

2. **How many years have you been treating squamous anal cancer?**

   a) < 5 years
   b) 5-10 years
   c) 11-15 years
   d) > 15 years

3. **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

4. **Is there a multidisciplinary tumor board for lower gastrointestinal cancers in your center?**

   a) yes
   b) no

5. **Members of the group (cross with an X also multiple answers):**

α) Surgeon
β) Oncologist Radiotherapist
χ) Medical Oncologist
δ) Radiologist
ε) Nuclear Doctor
ϕ) Pathologist
γ) Endoscopist
η) Gynecologist
ι) Other

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

α) TR ultrasound
β) Pan-colonoscopy
χ) CT scan abdomen
δ) EcoEndoscopy
ε) MRI pelvis
ϕ) Chest CT scan
γ) PET / CT
η) Chest x-ray
ι) Markers (CEA)
φ) Abdomen ultrasound
κ) MRI upper abdomen

7) The patients referred to your center have performed in the majority:

α) Surgery and CT-RT to follow
β) CT-RT exclusive
χ) Neoadjuvant CT-RT followed by surgery
δ) Rescue surgery after CT-RT
ε) Exclusive surgery

8) Which surgery is reserved for this type of patient?

α) local excision
β) low anterior resection
χ) mesorectal excision

δ) Miles

Session 2: PATIENT SET UP FOR RT-CT IN THE ADENOCARCINOMA OF THE ANUS

1) SET UP

α) Immobilization systems

β) Positioning: prone | __ |; supine | __ |

χ) Use of belly board

δ) Anal Repere

2) CT simulation with i.v. contrast medium?

Simulation CT / PET?

CT / MRI simulation?

3) Bladder filling protocol?

Session 3: VOLUMES of INTEREST

1) The prescription of the volumes follows

A) The AIRO Guidelines for squamous cell carcinoma of the anus

B) The AIRO guidelines for rectal cancer

C) Specific guidelines _____

2) In defining the areas at risk, do you maintain the distinction present in the AIRO guidelines for calcium in the anus (low, intermediate and high risk areas)?

Yes | __ | No | __ |

In case of positive answer

Define the low-risk area

- Primary tumor and anal canal | __ |
- mesoretto if N- (whole or partial) | __ |
- the ischio-rectal fossa (whole or partial) | __ |
- the presacral space | __ |
- the internal iliac lymph nodes | __ |
- the external iliac lymph nodes | __ |
- the inguinal lymph nodes | __ |
- the obturator lymph nodes | __ |
- the common iliac lymph nodes | __ |
- the common iliac lymph nodes only if N + to the external / internal | __ |

Define the intermediate risk area

- Primitive mood and anal canal | __ |
- mesoretto if N- (whole or partial) | __ |
- the ischio-rectal fossa (whole or partial) | __ |
- the presacral space | __ |
- the internal iliac lymph nodes | __ |
- the external iliac lymph nodes | __ |
- the inguinal lymph nodes | __ |
- the obturator lymph nodes | __ |
- the common iliac lymph nodes | __ |
- the common iliac lymph nodes only if N + to the external / internal | __ |

Define the high risk area

- Primary tumor and anal canal | __ |
- mesoretto if N- (whole or partial) | __ |
- the ischio-rectal fossa (whole or partial) | __ |
- the presacral space | __ |
- the internal iliac lymph nodes | __ |
- the external iliac lymph nodes | __ |
- the inguinal lymph nodes | __ |
- the obturator lymph nodes | __ |
- the common iliac lymph nodes | __ |
- the common iliac lymph nodes only if N + to the external / internal | __ |

3) What imaging do you use for the contouring of Volumes and OARs:

A. Diagnostic CT (1 = Always; 2 = In selected cases; 3 = Rarely; 4 = Never): | __ |

B. RM (1 = Always; 2 = In selected cases; 3 = Rarely; 4 = Never): | __ |

C. PET / CT (1 = Always; 2 = In selected cases; 3 = Rarely; 4 = Never): | __ |

4) Use image fusion (co-registration with simulation CT) (1 = No; 2 = Yes; 3 = on specific indication): _____

If so, what type: rigid | __ |; deformable | __ |

SESSION 4: RADIOTHERAPY

Using the TMN staging of the anus (American Joint Committee on Cancer (AJCC) 2010 edition).

1) Dose RT in T1N0 (insert numbers in the boxes):

- CTV 1 (high risk): total dose (Gy) | __ |, dose per fraction (Gy) | __ | Total number of fractions: | __ |, Number of fractions / week: | __ |

- CTV 2 (intermediate risk): total dose (Gy) | __ |, dose per fraction (Gy) | __ | Total number of fractions: | __ |, Number of fractions / week: | __ |

- CTV 3 (low risk): total dose (Gy) | __ |, dose per fraction (Gy) | __ | Total number of fractions: | __ |, Number of fractions / week: | __ |

2) Dose RT in T2N0 (insert numbers in the boxes):

- CTV 1 (high risk): total dose (Gy) | __ |, dose per fraction (Gy) | __ | Total number of fractions: | __ |, Number of fractions / week: | __ |

- CTV 2 (intermediate risk): total dose (Gy) | __ |, dose per fraction (Gy) | __ | Total number of fractions: | __ |, Number of fractions / week: | __ |

- CTV 3 (low risk): total dose (Gy) | __ |, dose per fraction (Gy) | __ | Total number of fractions: | __ |, N fractions / week: | __ |

17) Dose RT in T3-4 N + (insert numbers in the boxes):

- CTV 1 (high risk): total dose (Gy) | __ |, dose per fraction (Gy) | __ | Total number of fractions: | __ |, Number of fractions / week: | __ |

- CTV 2 (intermediate risk): total dose (Gy) | __ |, dose per fraction (Gy) | __ | Total number of fractions: | __ |, Number of fractions / week: | __ |

- CTV 3 (low risk): total dose (Gy) | __ |, dose per fraction (Gy) | __ | Total number of fractions: | __ |, N fractions / week: | __ |

3) How do you boost ?: SIB | __ |, Sequential | __ |, Concomitant | __ |

In case of concomitant specify No. fractions / week (daily, 2vv / week, other): _____

4) What techniques do you use in the RT-CT treatment? (also cross multiple answers with an X):

3DCRT | __ |

IMRT / VMAT | __ |

Brachytherapy (BRT) | __ |

IGRT | __ |

Combination of EBRT and BRT | __ |

Other_____

5) In case of IGRT

Kv | __ |

MV | __ |

CBCT | __ |

MVCT | __ |

- periodicity of checks _____

____

6) Chemotherapy concomitant with radiotherapy (indicate in the box if: 1 = No; 2 = Yes; 3 = in selected cases): | __ |

if Yes, Scheme (abbreviation) _____

_____

7) Would your center possibly be willing to participate in a national study protocol on the treatment of adenocarcinoma neoplasia of the anus? (Yes No):____

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