Cancer of the anal canal (cancer of the anus)

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Introduction

Generalities

The anal canal is the terminal part of the digestive tube, is 3–4 cm long, and located between the rectum and the skin at the anal verge. Tumors of the anal verge are classified with skin tumors (WHO).

Cancers of the anal canal are rare, predominate in women (M/F sex ratio, 0.4:4.4 in France) [3, 6]. They account for 1.2% of digestive cancers and 6% of rectoanal cancers [3]. Two-thirds of patients are 65 years old or older [6]. The incidence is increasing [8].

Epidermoid cancers of the anal canal account for 95% of anal canal cancer cases. Only 5% are metastatic at diagnosis [6].

Other than female sex and age, homosexuality, HPV infection, and smoking are risk factors.

Treatment aims to cure the patient and to obtain better local control by preserving sphincter function.

In the last few years, treatments preserving the sphincter have been developed; they use radiotherapy in association with concurrent chemotherapy for large tumors.

Histological diagnosis

Histological diagnosis distinguishes epidermoid cancers from other forms:

- Epidermoid cancers:
  - large-cell keratin-producing
  - non-keratin-producing (transitional)
  - basaloid
- Adenocarcinomas:
  - rectal type, anal glands
  - on anorectal fistula
- Small-cell carcinomas
- Undifferentiated carcinomas
- Other tumors (sarcomas, lymphomas, melanomas, etc.)

Prognostic factors

Knowing the prognostic factors helps better determine the place of the different treatments available in a multidisciplinary strategy.

Prognostic factors

ON SURVIVAL

The T stage is a prognostic factor for a number of authors [3, 5, 10, 13, 14, 16, 19].

For some, the size above or below 4 cm is also prognostic [5, 9, 10, 19].

Inguinal or pelvic lymph node invasion is also described [5, 9, 10, 13].

ON LOCAL-REGIONAL CONTROL

The only prognostic factor of local-regional control is the size of the primary tumor, which is not always found [3, 10, 16].

Other prognostic factors

PATIENT-RELATED

Advanced age and male sex have been found

HOMOSEXUALITY AND HIV INFECTION

Homosexuality and HIV infection have not been studied as a prognostic factor (too few patients). HIV infection is not a contraindication for curative treatment [4].

Staging

Staging occurs before beginning therapy, with the initial therapy usually conservative. The old 1967 UICC classification,
which was based on histological analysis of the operative specimen, has been abandoned.

References

Use the UICC clinical TNM classification (6th edition 2002):

### Primary tumor

- **T1**: tumor ≤2 cm at its greatest diameter
- **T2**: tumor >2 cm but ≤ 5 cm at its greatest diameter (21–50 mm)
- **T3**: tumor >5 cm at its greatest diameter
- **T4**: tumor, whatever its size, invading one or several adjacent organs (vagina, ureter, bladder) with the exception of the rectum, perineal skin, subcutaneous cell tissue, and sphincter.

### Regional adenopathy (N)

- **Nx**: lymph nodes not evaluated
- **N0**: no lymph node metastasis
- **N1**: perirectal lymph nodes
- **N2**: internal iliac and/or unilateral inguinal lymph nodes
- **N3**: perirectal and inguinal and/or bilateral internal iliac lymph nodes and/or bilateral inguinal.

- **NB**: number of lymph nodes to examine histologically: at least 12 in perirectal and pelvic lymph node removal and at least 6 for inguinal removal. If the lymph nodes examined are not affected, even if this number has not been reached, class pN0.

### Distant metastases (M)

- **MX**: not evaluated
- **M0**: no metastasis
- **M1**: distant metastases

### Alternatives

These classifications are used in certain large series, based on the argument that they are more representative of prognostic factors.

### Other clinical classifications

#### Diagnosis: Reference

- Clinical examination and forceps biopsy and pathological analysis

#### Local-regional extension workup

Objectives: describe the sites of tumor extension so as to adapt treatment to prognostic factors and limit the volume of tissue irradiated.

References

Clinical: anorectal digital examination may be done with general anesthesia, preceded by examination of the anal verge, flattening the transverse folds, evaluates the tumor’s extension in terms of height, its extension in relation to the anal verge, and the anorectal transition zone, and invasion of the lower rectum.

It identifies the circular extension, its fixation to the anococcygeal space and to the ischioanal fossae, and its relations with the prostate or vagina. This examination can identify perirectal adenopathy.

In the anterior forms, digital and speculum vaginal examinations are necessary. The inguinal areas are palpated looking for adenopathy, which are sampled by needle biopsy.

A gynecological exam with verge smear is necessary in the search for associated HPV lesions.

Anoscopy completes the digital rectum examination.

The general examination searches for a pelvic mass, hepatomegaly, and supraclavicular adenopathy.

The paraclinical workup includes a chest x-ray and a pelvis and liver CT scan.

### Echocendoscopic classification

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### Table: Comparison of Classification Systems

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<tbody>
<tr>
<td><strong>T1</strong></td>
<td></td>
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<tr>
<td>&lt;3 cm</td>
<td>≤1/3 of the length or circumference of the anal canal</td>
<td>Same</td>
<td>&lt;2 cm</td>
<td>&lt;2 cm</td>
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<tr>
<td><strong>T2</strong></td>
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<tr>
<td>3–6 cm</td>
<td>&gt;1/3 of the length or circumference of the anal canal or infiltrating the external sphincter</td>
<td>Same</td>
<td>2-4 cm</td>
<td>2.5 cm</td>
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<td><strong>T3</strong></td>
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<tr>
<td>&gt;6 cm</td>
<td>Spread to the skin or rectum</td>
<td>Same</td>
<td>&gt;4 cm</td>
<td>&gt;5 cm</td>
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<tr>
<td>- T3a &lt;4 cm</td>
<td>mobile, no vaginal extension, &lt;2/3 of anal circumference</td>
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<td>- T3b &gt;4 cm</td>
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<tr>
<td><strong>T4</strong></td>
<td>Invasion of neighboring organs</td>
<td>Invasion of neighboring structures</td>
<td>Invasion of neighboring organs</td>
<td>Invasion of neighboring organs</td>
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<tr>
<td>- T4a: vagina and/or vulva</td>
<td>- T4a: vaginal extension &gt; 2/3 of circumference of the anal canal</td>
<td>- T4b: other neighboring structures excluding vagina or rectum; or fixed tumor</td>
<td>- T4b: other neighboring structures</td>
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Alternatives

**ENDORECTAL ULTRASOUND OR ECHOENDOSCOPY CAN BE DONE**

- determine the maximum thickness of the tumor and invasion of layers
- search for perirectal and rectosigmoid adenopathy
- determine the local extension according to the table below (us-TN)
  - usT1: mucosa and submucosa involvement with no involvement of the internal sphincter muscle
  - usT2: involvement of the internal sphincter muscle with no involvement of the external sphincter muscle
  - usT3: involvement of the external sphincter muscle
  - usT4: involvement of a neighboring organ
- usN0: no suspicious adenopathy
- usN+: perirectal adenopathy 5–10 mm in diameter with malignant characteristics (round, hypoechogenic, clear contours) or measuring more than 10 mm in diameter.

Therapeutic methods

Therapy aims to obtain a high rate of survival and the best local and regional control possible. The sphincter and sphincter function preservation rates are also evaluated.

For limited forms, treatment is based on radiotherapy and for extended forms it is based on associating radiotherapy and chemotherapy and/or surgery.

Surgery

- Anorectal resection via the abdominoperineal approach with upper, middle, and lower hemorrhoidal lymph node removal.
- Necessary inguinal lymph node removal is intentionally limited to excision when there are malignant or suspicious adenomas. It can be done before or after inguinal irradiation. It exposes the patient to the onset of persistent lymphocele and to the appearance of a lymphoedema.
- Local excision is an option for tumors that appear to be benign or in situ, or more rarely for small T1 tumors less than 1 cm at its largest diameter.

Exclusive radiotherapy

Split course radiotherapy consists of a first series of external radiotherapy followed, after a rest period, by complementary external radiotherapy or interstitial curietherapy.

The first period of radiotherapy consists of posterior pelvic irradiation whose target volume includes the verge, the canal, the lower rectum, and the perirectal and lateral pelvic lymph nodes.

It is performed with the patient in the dorsal or ventral decubitus position by rays 10 MV delivered in three or four beams. It delivers 50 Gy in 25 fractions in 5 weeks.

Unilateral or bilateral lymph node areas can be added to the target volume, which means the technique must be adapted by using an additional anterior direct field of 6- to 12-MV electrons.

The second irradiation period (complementary) can be delivered by external radiotherapy or iridium interstitial curietherapy on the initial tumor volumes at a dose of 15–20 Gy.

Exclusive chemotherapy

Combining 5 Fluorouracil (600–1000 mg/m² from D1 to D4 or D5) and mitomycin C (10–15 mg/m² on D1) is the reference, renewed every 28 days.

Combining 5 Fluorouracil (600–1000 mg/m² from D1 to D4 or D5) and cisplatin (80–100 mg/m² in one injection or over 5 days) can be an alternative.

There does not seem to be any crossed resistance.

Radiochemotherapy treatment

Radiochemotherapy treatment combines pelvic external radiotherapy (45 Gy in 25 fractions and 5 weeks) and concurrent chemotherapy the 1st week (and optionally the 5th week) according to the 5FU–mitomycin C, or 5FU–cisplatin.

Induction chemotherapy is used by some with a high level of response.

Radiosurgical treatment

Preoperative pelvic radiotherapy or preoperative radiochemotherapy is followed by abdominoperineal resection after 6 weeks.

Therapeutic indications

Objectives

- Cure the patient by obtaining local and regional control of the disease.
- Cure the patient by preserving a functional anus.
- Prevent metastatic progression.

Three trials have demonstrated the superiority of combining radiotherapy and chemotherapy with 5FU–mitomycin C over radiotherapy alone for locally advanced tumors, with an increase in local control and survival without colostomy, but without benefit for overall survival [1, 7, 18].

Abdominoperineal resection is reserved for failure of conservative treatment or for serious complications.

T1 N0 stages

Reference

Conservative treatment (level of evidence A)
Exclusive radiotherapy (level of evidence B)
50 Gy / 25 fractions / 5 weeks, then complement

**Alternative**
Excision surgery for in situ tumors of at least 1 cm

**T2 N0 stage**

**Reference**
Conservative treatment (level of evidence A)
Exclusive radiotherapy (level of evidence A)
50 Gy / 25 fractions / 5 weeks, then localized complement

**Alternative**
Alternative = FFCD 9804 – accord 03 therapeutic trial (inclusions ended)
Concurrent and/or neoadjuvant chemotherapy for tumors larger than 4 cm at greatest size (level of evidence D)

**T3 or T1–T2 N1 - N3 stages**

**Reference**
Exclusive concurrent radiochemotherapy (5FU–mitomycin C),
45 Gy / 25 fractions / 5 weeks, then localized complement (level of evidence A).

**Alternative**
- Radiochemotherapy and then mutilating surgery if there is no tumor response
- Concurrent radiochemotherapy (5FU–cisplatin) or neoadjuvant radiochemotherapy (level of evidence D) = FFCD 9804 – ACCORD 03 therapy trial (inclusions ended)

**T4 stages**

**Reference**
None

**Alternatives**
- Exclusive radiochemotherapy
- Radiochemotherapy and surgery

**Tumors that are immediately metastatic**

**Reference**
None

**Alternatives**
- Exclusive chemotherapy (level of evidence D).

**Monitoring**

Monitoring has a double objective:
- Screen for local and regional recurrence or metastases that can be treated so as to obtain cure or increase survival.
- Detect local complications related to conservative treatment and prevent mutilation.

80% of recurrences occur within 48 months after treatment, distributed in:
- Isolated local recurrences
- Local-regional recurrences
- Metastatic recurrences
- One-third or one-half of local of local-regional recurrences can be treated, generally with abdominoperineal resection
- The frequency of local recurrences is:
  - 0%–20% for T1 tumors
  - 10%–30% for T2 tumors
  - 20%–40% for T3 and T4 tumors
- The frequency of complications is 5%–10% for T1 and T2 tumors and 15%–30% for T3 and T4 tumors after conservative treatment.
- Monitoring is difficult because the anal canal has been modified after conservative treatment and because of the local complications that can lead to repeated follow-up biopsies.

**Reference**
Clinical examination with pelvic exam, anoscopy, inguinal palpation, every 4 months for 2 years, then every 6 months for 3 years, and then annually
- Biopsies should be avoided because of the risk of necrosis after radiotherapy.

**Alternatives**
- When there is advanced local tumor from the beginning, an abdominopelvic CT and a chest x-ray should be done.

**REFERENCES**


