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Radiotherapy

The Role of Radiotherapy in the Management of Anal Canal Cancer: A Retrospective Study of 44 Cases from Hassan II University Hospital, Fez, Morocco

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Abstract | **Original Research Article**

Anal canal cancer is a rare malignancy whose treatment relies on radiotherapy, most often combined with concurrent chemotherapy. This retrospective study included 44 patients with histologically confirmed anal canal cancer treated in the radiotherapy department of Hassan II University Hospital, Fez, Morocco, between January 2012 and January 2024. The mean age was 65 years (range 30–86) and 61% of patients were men. The mean delay before consultation was 10 months. Rectal bleeding was the most frequent presenting symptom (59%), followed by deterioration of general condition (45%) and an anal mass (43%). Squamous cell carcinoma accounted for 75% of cases. Among the 30 patients with complete staging, 83% had T3–T4 tumours and 83% had nodal involvement. Radiotherapy was delivered with curative intent in 40 patients (91%) and with palliative intent in 4 (9%); it was combined with concurrent chemotherapy in 34 patients (77%) and given alone in 6 (14%). The total dose ranged from 45 to 60 Gy, delivered by three-dimensional conformal radiotherapy in all patients but one. Concurrent chemotherapy was mainly 5-fluorouracil and cisplatin (29 patients). Acute radiation toxicity occurred in 29 patients (66%), dominated by radiodermatitis (23 cases, grade 3 in 8). Twelve patients were lost to follow-up. Among the 32 patients with a known outcome, overall survival at last follow-up was 72% and disease-free survival 31%; 9 patients died and 13 had progression, recurrence or metastases. Anal canal cancer is diagnosed late and at an advanced stage in our setting, limiting the results of chemoradiotherapy. Earlier diagnosis, wider access to pelvic MRI and intensity-modulated radiotherapy, and closer follow-up are needed.

Keywords: Anal canal cancer, Squamous cell carcinoma, Radiotherapy, Chemoradiotherapy, Cisplatin, 5-fluorouracil, Abdominoperineal resection, Morocco.

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INTRODUCTION

Anal canal cancer is a rare tumour, representing a small fraction of digestive malignancies, but its incidence has been rising steadily in many countries over recent decades [1, 2]. Squamous cell carcinoma is by far the predominant histological type, and persistent infection with high-risk human papillomavirus is found in the great majority of cases [3]. Other recognised risk factors include tobacco smoking, sexual practices that favour HPV transmission and immunosuppression [4]. Until the 1970s, abdominoperineal resection with permanent colostomy was the reference treatment. The work of Nigro and colleagues showed that radiotherapy combined with 5-fluorouracil and mitomycin could eradicate the tumour while preserving the anal sphincter [5]. Randomised trials later confirmed the superiority of concurrent chemoradiotherapy over radiotherapy alone for local control and colostomy-free survival [6–8]. Chemoradiotherapy is now the standard of care for localised disease, and surgery is reserved for persistent or recurrent tumours [1]. Data from North Africa remain scarce. The aim of this study was to describe the epidemiological, clinical, therapeutic and evolutionary profile of patients treated with radiotherapy for anal canal cancer in our department, and to compare our results with the literature.

MATERIALS AND METHODS

Study design and setting.

This was a retrospective descriptive study conducted in the Department of Radiotherapy of Hassan

II University Hospital, Fez, Morocco, covering a 12-year period from January 2012 to January 2024.

Patients.

We included all patients with a primary anal canal cancer confirmed by histology and documented by imaging, who received radiotherapy as part of their management and whose medical record was usable for clinical, paraclinical, therapeutic and follow-up data. Patients with incomplete or unusable records were excluded. Patients irradiated with palliative intent and those with metastases at diagnosis were kept in the analysis, in order to describe all the indications of radiotherapy in our practice. Forty-four patients met these criteria.

Data collection.

Data were extracted from the department's hospital registry and from the hospital information system (HOSIX) using a pre-established form. The variables collected were epidemiological (age, sex, medical history, risk factors), clinical (consultation delay, symptoms, proctological examination), histological, radiological (pelvic MRI, thoraco-abdomino-pelvic CT), therapeutic (radiotherapy, chemotherapy, surgery, toxicity) and evolutionary. Tumours were staged according to the AJCC/UICC TNM classification, 8th edition (2017).

Treatment.

Planning was based on a dosimetric CT scan with the patient supine, arms on the chest, with knee and foot supports. Target volumes covered the primary tumour, the anal canal and the pelvic and inguinal lymph node areas. Follow-up consisted of a first visit 4 to 6 weeks after the end of treatment, then every 3 months for 2 years, every 6 months until the fifth year and yearly thereafter. It relied on clinical examination with digital rectal examination and inguinal palpation, complemented by pelvic or thoraco-abdomino-pelvic CT according to symptoms.

Statistical analysis.

Data were entered and analysed with Microsoft Excel. Results are expressed as numbers, percentages, means and ranges. Percentages of symptoms are calculated on the number of patients. Because dates of events and of last follow-up were not available for every patient, survival is reported as observed rates at last follow-up among patients with a known outcome: overall survival is the proportion of patients alive, and disease-free survival the proportion alive in complete remission. Actuarial (Kaplan–Meier) estimates could not be calculated.

Ethical considerations.

Data were collected anonymously and confidentially from medical records. This work was carried out as part of a doctoral thesis in medicine, defended publicly in February 2025 at the Faculty of Medicine, Pharmacy and Dental Medicine of Fez. Given its retrospective, non-interventional design based on anonymised records, no specific ethics committee approval was sought.

RESULTS

Epidemiological profile

Forty-four patients were treated over 12 years, with a maximum of 6 new cases per year (in 2016, 2019, 2020 and 2021). The mean age was 65 years (range 30–86), and the 60–69 age group was the most affected. There were 27 men and 17 women, giving a male-to-female ratio of 1.6. Fifteen patients (34%) had a history of benign anal disease, most often anal fistula. Chronic smoking was reported in 16 patients (36%) and chronic alcohol use in 2. Two patients had positive syphilis and hepatitis B serology. Thirteen patients (30%) had medical comorbidities, mainly hypertension (6) and diabetes (3).

Table 1: Characteristics of the 44 patients

Characteristic	Number	%
Age 30–39 years	3	7
Age 40–49 years	1	2
Age 50–59 years	6	14
Age 60–69 years	16	36
Age 70–79 years	14	32
Age 80–89 years	4	9
Male sex	27	61
Female sex	17	39
History of anal fistula	7	16
History of haemorrhoids	3	7
History of anal abscess	3	7
Pilonidal sinus	1	2
Anal condyloma	1	2
Chronic smoking	16	36

Clinical presentation

The mean delay between the first symptom and the first consultation was 10 months (range 2 months to 5 years). Seventeen patients (39%) consulted within 6 months, 15 (34%) between 7 and 12 months, and 12 (27%) after more than one year. Rectal bleeding was the leading symptom, present in 26 patients (59%). General condition was preserved (WHO performance status 1) in 34 patients (77%).

Table 2: Presenting symptoms (several symptoms possible per patient)

Symptom	Number	% of patients
Rectal bleeding	26	59
Deterioration of general condition	20	45
Protruding anal mass	19	43
Pelvic pain	13	30
Purulent discharge	10	23
Rectal syndrome	10	23
Constipation	6	14
Anal incontinence	3	7
Anal pruritus	1	2

On proctological examination, the tumour was ulcerated and exophytic in 28 patients (64%), exophytic in 10 (23%) and ulcerated in 6 (14%). The mean tumour size was 4 cm (range 2–15 cm). Sphincter tone was normal in 40 patients and reduced in 4. Clinical examination found invasion of the sphincter apparatus in 10 patients, extension to the rectovaginal septum in 4 and to the vagina in 2. Inguinal lymph nodes were palpable in 14 patients (32%), bilaterally in 10 and unilaterally in 4.

Histology and staging

Squamous cell carcinoma was the most frequent histological type (33 cases, 75%; Figure 1), followed by mucinous adenocarcinoma (7 cases, 16%), basaloid carcinoma (2 cases, 4.5%) and melanoma (2 cases, 4.5%). Tumours were well differentiated in 46% of cases, moderately differentiated in 29% and poorly differentiated in 25%.

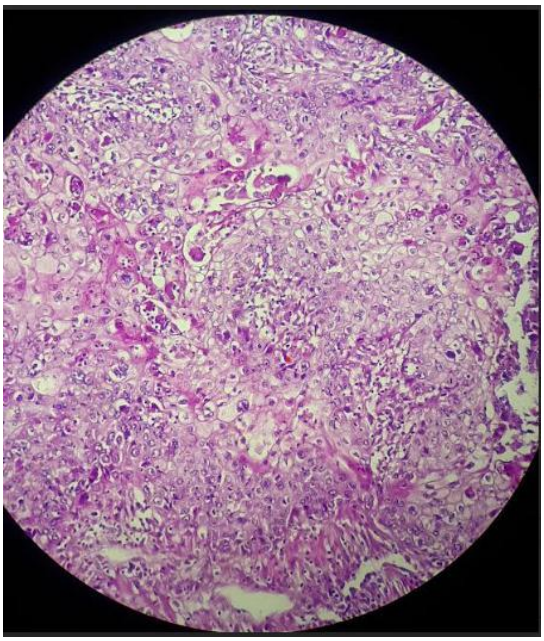


Figure 1: Microscopic appearance of a squamous cell carcinoma of the anal canal: large eosinophilic squamous cells arranged in rounded nests (haematoxylin and eosin stain). Source: Hassan II University Hospital, Fez.

Thoraco-abdomino-pelvic CT was performed in 31 patients (70%) and pelvic MRI in 13 (30%); access to MRI was limited by cost. One patient had a PET-CT and none had endoanal ultrasound. Imaging showed inguinal lymph nodes in 15 patients, mesorectal nodes in 12, external iliac nodes in 6, extension to the lower rectum in 5 and invasion of the sphincter apparatus in 6. Hypochromic microcytic anaemia was found in 13 patients (30%), with a mean haemoglobin level of 10 g/dL.

Complete TNM staging was available for 30 patients. T3 and T4 tumours together represented 83% of

staged cases, and 83% had nodal involvement. Three patients had distant metastases at diagnosis.

Treatment

The mean interval between diagnosis and the start of treatment was 4 months (range 2–10). Radiotherapy was delivered with curative intent in 40 patients (91%) and with palliative intent in 4 (9%). It was combined with concurrent chemotherapy in 34 patients (77%) and given alone in 6 (14%), when age, comorbidities or general condition precluded chemotherapy.

The total dose ranged from 45 to 60 Gy, with conventional fractionation of 1.8 to 2 Gy per fraction, 5 fractions per week. A boost of 20 Gy was delivered to the anal canal, and an inguinal boost of 14 Gy was added in case of palpable inguinal nodes. The median overall treatment time was 60 days (range 30–105), with no planned gap between the two sequences. Three-dimensional conformal radiotherapy was used in all patients except one, who received intensity-modulated radiotherapy (IMRT). No patient received brachytherapy. An example of target volume delineation is shown in Figure 2.

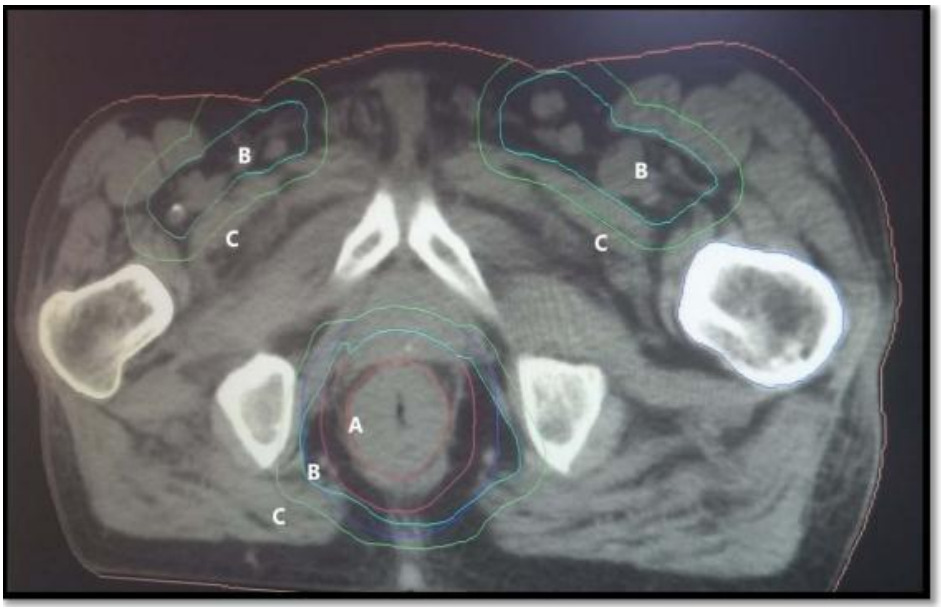


Figure 2: Delineation of target volumes on the planning pelvic CT scan. A: gross tumour volume (GTV); B: clinical target volume (CTV), covering the anal canal and the inguinal lymph node areas; C: planning target volume (PTV). Source: Department of Radiotherapy, Hassan II University Hospital, Fez.

Concurrent chemotherapy combined 5-fluorouracil (800 mg/m² on days 1 to 4) and cisplatin (75 mg/m² on day 1) in 29 patients, with a mean of 3 cycles. Five patients received paclitaxel as a single agent (175 mg/m² on day 1).

Table 3: Treatment modalities

Modality	Number	%
Concurrent chemoradiotherapy	34	77
Radiotherapy alone (curative intent)	6	14
Palliative radiotherapy	4	9
Upfront abdominoperineal resection	2	5
Salvage abdominoperineal resection after progression	1	2
Diverting colostomy	5	11
Local excision with inguinal node resection	3	7

Toxicity

Twenty-nine patients (66%) developed acute radiation toxicity: radiodermatitis in 23 (grade 1 in 6, grade 2 in 9 and grade 3 in 8), radiation proctitis in 3 and radiation cystitis in 3. Chemotherapy toxicity was mainly haematological, with anaemia in 10 patients and afebrile neutropenia in 4. Peripheral neuropathy occurred in 5 patients, nausea and vomiting in 4, and deep vein thrombosis in 1.

Outcomes

Ten patients (23%) achieved complete remission and remained under annual surveillance. Among 10 patients with inguinal lymph node involvement, 5 reached complete remission after

concurrent chemoradiotherapy. Four patients progressed immediately after the end of treatment; one underwent abdominoperineal resection and three received chemotherapy. Four patients had a locoregional recurrence, occurring 6 to 24 months after treatment. Five patients developed distant metastases, in the lung in 4 cases (2 years after treatment) and in the sacroiliac region in 1. Nine patients died and 12 were lost to follow-up. Of the 6 patients treated with radiotherapy alone, 4 were lost to follow-up.

Table 4: Outcomes at last follow-up

Outcome	Number	%
Complete remission	10	23
Progression immediately after treatment	4	9
Locoregional recurrence	4	9
Distant metastases	5	11
Death	9	20
Lost to follow-up	12	27

Survival

The outcome was known for 32 of the 44 patients (73%). At last follow-up, 23 of them were alive, giving an overall survival of 72%. Ten were alive in complete remission, giving a disease-free survival of 31%. The remaining 13 living patients had persistent, recurrent or metastatic disease. If the 12 patients lost to follow-up are counted as failures, the disease-free rate falls to 23% (10 of 44). All documented complete remissions occurred in patients treated with concurrent chemoradiotherapy: 10 of 34 (29%).

DISCUSSION

This series of 44 patients shows that, in our setting, anal canal cancer is diagnosed late, at a locally advanced stage, and that outcomes after radiotherapy remain below those reported in reference series.

Epidemiology.

The mean age of our patients (65 years) is close to that of European series, where the median age ranges from 62 to 66 years [9–11]. In contrast, the male predominance observed here (sex ratio 1.6) differs from most Western series, in which women are more often affected [1, 2]. More than a third of our patients were smokers, a recognised risk factor for anal cancer [4]. HPV and HIV status were not documented in the records, which prevents any analysis of these factors, although HPV is detected in more than 80% of anal carcinomas [3].

Diagnostic delay and stage.

The mean consultation delay was 10 months, and more than a quarter of patients consulted after one year. Symptoms are non-specific and often attributed to benign anal disease, which 34% of our patients had previously experienced. This delay explains the advanced stage at diagnosis: 83% of our staged patients had T3–T4 tumours and 83% had nodal involvement. In published series, T1–T2 tumours are the most frequent (T2 in 60% of patients for Lerman *et al.,* and 46% for Claren *et al.,*) and nearly 60% of patients are node-negative [9, 11]. A Chinese multicentre series also reported fewer advanced tumours than ours, with T3–T4 in 44% of cases [12]. Limited access to pelvic MRI, performed in only 30% of our patients, is another weakness, since MRI is the reference examination for locoregional staging [1].

Radiotherapy and chemotherapy.

Concurrent chemoradiotherapy has been the standard treatment since randomised trials showed its superiority over radiotherapy alone. In the UKCCCR ACT I trial, adding 5-fluorouracil and mitomycin reduced local failure at 3 years from 59% to 36% [6]. The EORTC trial reported an 18% gain in locoregional control and a 32% gain in colostomy-free survival at 5 years [7]. The RTOG 87-04 trial then established the contribution of mitomycin [8]. In our department, 77% of patients received concurrent chemotherapy, mainly with 5-fluorouracil and cisplatin. The ACT II trial found no significant difference in complete response between cisplatin and mitomycin given concurrently [13], whereas the RTOG 98-11 trial, which used induction cisplatin, favoured the mitomycin arm for disease-free and overall survival [14]. Mitomycin with 5-fluorouracil therefore remains the preferred regimen in current guidelines [1].

The doses delivered in our series (45 to 60 Gy) are in line with recommendations. However, the median overall treatment time was long (60 days, up to 105 days). Pooled data from the RTOG 87-04 and 98-11 trials showed that prolonged treatment time is associated with poorer local control [15]. Nearly all our patients were treated with three-dimensional conformal radiotherapy. Grade 3 radiodermatitis occurred in 8 patients (18% of the series). The RTOG 0529 trial showed that IMRT reduces acute skin, digestive and haematological toxicity compared with conventional techniques [16]. IMRT is now the recommended technique, and its wider use in our department should reduce toxicity and treatment interruptions [1].

Outcomes.

Only 23% of our patients were in documented complete remission, and 10 of the 34 patients treated with chemoradiotherapy (29%) were locally controlled.

In the ACT II trial, the complete response rate at 26 weeks was about 90% [13]. Several factors explain this gap: the predominance of T3–T4 and node-positive tumours, the inclusion of non-squamous histologies (adenocarcinoma and melanoma), which respond poorly to chemoradiotherapy, the long treatment time and, above all, the high proportion of patients lost to follow-up (27%), whose response could not be assessed. Tumour regression after chemoradiotherapy is slow, and response should be assessed up to 26 weeks before salvage surgery is considered [17]. Abdominoperineal resection, performed after progression in one of our patients, remains the salvage treatment for persistent or recurrent disease [1]. Finally, adherence to treatment guidelines has been shown to improve overall survival markedly in anal cancer [18].

Overall survival.

Among our patients with a known outcome, overall survival at last follow-up was 72% (23 of 32). This figure must be read with caution: it is not an actuarial estimate, follow-up durations were heterogeneous, and the 12 patients lost to follow-up may include unrecorded deaths. With this reservation, it lies below the results of the large trials. In the RTOG 98-11 trial, 5-year overall survival was 78.3% with 5-fluorouracil and mitomycin and 70.7% with 5-fluorouracil and cisplatin [14]. The 13-year update of the ACT I trial confirmed a lasting benefit of chemoradiotherapy, with 12.5 fewer deaths from anal cancer for every 100 patients treated compared with radiotherapy alone [19]. Survival depends strongly on stage: in RTOG 98-11, 5-year overall survival fell from 82% for T2N0 tumours to 42% for T4 node-positive tumours [20]. As 83% of our staged patients had T3–T4 tumours and 83% had nodal involvement, our population corresponds to the least favourable subgroups of these trials.

Disease-free survival.

Disease-free survival at last follow-up was 31% among patients with a known outcome (10 of 32), and 23% if patients lost to follow-up are counted as failures. In RTOG 98-11, 5-year disease-free survival was 67.8% in the mitomycin arm and 57.8% in the cisplatin arm [14], and in ACT II, 3-year progression-free survival was close to 74% [13]. Here again, stage is decisive: 5-year disease-free survival in RTOG 98-11 ranged from 72% for T2N0 to 31% for T4 node-positive disease [20]. Our disease-free rate is therefore comparable to that of the most advanced tumours in the literature, and well below that of early-stage disease. Most failures in our series were early: 4 patients progressed immediately after treatment and 3 of the 4 locoregional recurrences occurred within the first year, which matches the known pattern of relapse, predominantly locoregional and within 2 years.

Prognostic factors.

Our series combines several factors known to worsen survival. Analysis of RTOG 98-11 identified male sex, tumour diameter above 5 cm and clinically positive nodes as independent predictors of poorer disease-free and overall survival [21]. The mature results of ACT I likewise found male sex, palpable nodes and low haemoglobin to be associated with a higher risk of locoregional failure and death [22]. In our series, 61% of patients were men, 32% had palpable inguinal nodes and 30% were anaemic at diagnosis. Smoking, reported by 36% of our patients, has also been studied as a factor of poorer outcome after chemoradiotherapy [9].

Non-squamous histologies.

Nine of our 44 patients (20%) had a non-squamous tumour: 7 had adenocarcinoma and 2 had melanoma. The evidence supporting exclusive chemoradiotherapy concerns squamous cell carcinoma. Anal adenocarcinoma is usually managed like low rectal cancer, with surgery after neoadjuvant treatment, and anal melanoma has a poor prognosis whatever the treatment. Their inclusion contributes to the low rates of complete remission and survival in our series, and one of the 3 abdominoperineal resection specimens showed melanoma.

Recurrent and metastatic disease.

Thirteen of our patients had progressive, recurrent or metastatic disease, and only one could undergo salvage abdominoperineal resection. Salvage surgery is the only curative option for isolated locoregional failure, but it requires early detection, which close follow-up during the first 2 years is meant to provide [1]. For metastatic or unresectable disease, the InterAACT trial has established carboplatin with paclitaxel as a reference first-line regimen, with a median overall survival of 20 months compared with 12.3 months for cisplatin with 5-fluorouracil, and less toxicity [23].

These results should be interpreted in light of the retrospective, single-centre design of the study and its small sample size. The number of patients lost to follow-up did not allow actuarial survival analysis, and a prospective registry with dated follow-up would give more precise estimates.

CONCLUSION

Anal canal cancer remains rare, but in our context it is diagnosed late and at a locally advanced stage, which compromises the results of conservative treatment. Radiotherapy, combined with concurrent chemotherapy whenever possible, is the cornerstone of management and allows sphincter preservation. Improving outcomes requires earlier diagnosis through systematic digital rectal examination and biopsy of any suspicious anal lesion, wider access to pelvic MRI and IMRT, shorter overall treatment times, and structured

follow-up to reduce the number of patients lost to follow-up. HPV vaccination and screening of precancerous lesions in at-risk populations are the basis of prevention.

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