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Radio-chemotherapy in anal cancer: Institutional experience at a large radiation oncology center in Chile

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ABSTRACT

Aim: In this article the aim is to provide a concise narrative review and inform the institutional experience at a referral center in Chile with the use of radio-chemotherapy in anal cancer.

Background: Cancer of the anus and anal canal is mainly a loco-regional disease. For years the standard of care has been concomitant radio-chemotherapy, which permits organ preservation and better local control than alternative surgical procedures.

Materials and methods: A retrospective analysis of 44 patients treated between 2002 and 2010 was performed. Local recurrence, distant recurrence and overall survival were analyzed with the Kaplan–Meier method. Relevant groups where compared with the log-rank test and univariate analysis were done with the Cox proportional hazards model.

Results: Median follow-up of the cohort was 56 months, with a minimum follow-up of at least 24 months. There was a significant difference between clinical stages in disease free survival (log-rank trend $p < 0.001$), and a significant difference in overall survival (OS) when comparing clinical stages that were grouped in stage I–IIIa and IIIB (log-rank $p = 0.001$). On univariate analysis, age older than 60, having received full treatment and dose above 45 Gy were all significantly related to OS ($p < 0.05$). An overall survival of 45% and disease free survival of 45% at 5 years were found in our series.

Conclusions: Our findings show that results at the Instituto de Radiomedicina in Chile are comparable to published literature. Dismal results in stage IIIb cases indicate much work remains in therapies to achieve loco-regional control in locally advanced cases.

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1. Background

The Chilean Ministry of Health, in its first report of population cancer registries, estimates an annual incidence of rectal and anal cancer of 4.4 cases per 100,000 people, with approximately 790 new cases diagnosed yearly. The adjusted death rate is 4.9 deaths per 100,000 people, with an estimated number of 480 annual deaths.[1] Disaggregated data of these diseases do not exist in Chile. Data from the US indicate that the median age at diagnosis before 2009 was 60 years of age, with 51% of them being diagnosed between 45 and 64. Most of the cases are diagnosed in a localized stage (49%) or with regional spread (30%), and only 13% have distant metastases at the time of diagnosis or stage is unknown (8%). Overall 5-year survival reaches 65%, varying widely between stages, from 79% to 30% in localized and metastatic disease, respectively.[2,3]

The symptoms of anal cancer are not unique and are also symptoms of other conditions, such as hemorrhoids. Symptoms may include lumps or bumps located near the anus, anal bleeding or bleeding during bowel movements, anal discharge, pain in or around the anus, itchy sensation around or inside the anus, change in bowel habits, such as constipation, diarrhea and thinning of the stools or para-neoplastic syndrome.[4]

Due to the low frequency of distant metastases at the time of diagnosis, anal cancer is considered mainly a loco-regional disease, making concomitant radio-chemotherapy an ideal organ and function sparing treatment which has been the standard of care for decades, with excellent results even in locally advanced tumors. Since the 1980s, many attempts have been made to improve loco-regional control and reduce toxicity, evaluating the role of mitomycin and investigating the role of IMRT.

In this article, the objective is to describe the results of treatment for anal cancer at a large radiation oncology center in Chile, identifying relevant prognostic factors in these cohort of patients.

2. Materials and methods

The Institute of Radiation Medicine (IRAM) is the largest private radiation oncology center in Chile, and it provides services to a large number of patients from the public health sector, approximately 3000 annually. All treatment decisions are made in multidisciplinary tumor boards.

Between 2002 and 2010, 44 patients were treated at the IRAM with the diagnosis of cancer of the anal canal. The treatment delivered was concomitant radio-chemotherapy, with 45 Gy in 25 daily fractions and 1000 mg/m^2 of 5-FU, days 1–4, and 10 mg/m^2 of mitomycin, day 1 the 1st and 5th week of treatment. An AP field was used that includes the pelvis, anus and inguinal lymph nodes, with the superior border at L5-S1 and the inferior border including the anus with a 2 cm margin. Lateral borders include the inguinal lymph nodes determined by bony landmarks. After an initial dose of 30.6 Gy in 17 fractions the superior extent of the field is reduced to the bottom of the sacroiliac joints, completing another 14.4 Gy in 8 fractions. Patients with clinically negative inguinal nodes also have a field reduction of this area at 30.6 Gy. According to clinical response, patients may receive a 9 Gy boost to the primary tumor. CT planning was standard in all patients.

Table 1 – Patient characteristics.

Characteristics	No. of patients (%)
Median age (range)	62 (28–63)
Sex	
Male	12 (27)
Female	32 (73)
HIV status	
Positive	6 (14)
Negative	38 (86)
Histological grade	
1	2 (5)
2	22 (50)
3	20 (45)
T stage	
1	5 (11)
2	12 (27)
3	14 (32)
4	13 (30)
N stage	
0	23 (53)
1	9 (20)
2	12 (27)
Stage (AJCC 2003)	
I	6 (14)
II	13 (30)
IIIA	9 (20)
IIIB	16 (36)
Karnofsky score	
70	4 (9)
80	6 (14)
100	34 (77)

2.1. Statistical analysis

Descriptive statistics for the analysis were proportions, medians and ranges where appropriate. The Kaplan–Meier method was used to estimate survival and graph survival curves. Log-rank tests where used to compare time to event outcomes between groups. Cox proportional hazards model was used for univariate analysis, with $p < 0.05$ considered statistically significant. All analyses where done in STATA 12 (College Station, Texas).

3. Results

Median follow-up of the cohort was 56 months, with a minimum follow-up of at least 24 months. Table 1 shows the characteristics of this cohort of patients.

A total of 8 patients experienced loco-regional recurrence after treatment; in 5 of them it was the only site of failure. Nine patients had a distant failure, 6 of them with only a distant failure. In total, 14 patients had a recurrence, with 3 of them having both loco-regional and distant failures. Of the 8 loco-regional failures, 6 occurred in the first three years, while 5 of the 6 distant failures occurred in the same period of time. Median disease free survival (DFS) defined as loco-regional failure, distant failure or death for the entire population was 50 months. DFS at 3 and 5 years was 60% and 45%, respectively (Fig. 1).

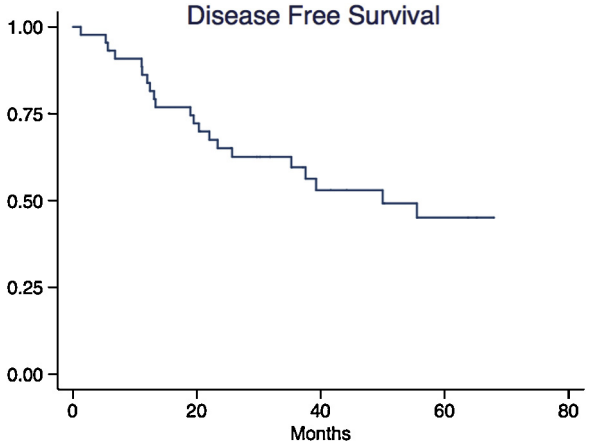

Fig. 1 – Kaplan–Meier curves for disease free survival for all patients.

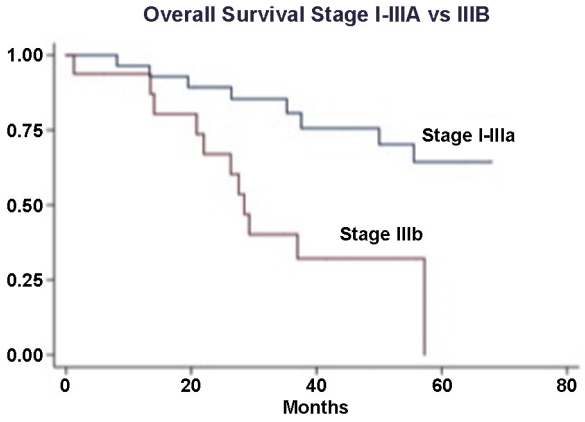

Fig. 3 – Kaplan–Meier curves for overall survival according to stage.

Median overall survival (OS) for the entire cohort was 57 months. OS at 3 and 5 years was 66% and 47%, respectively (Fig. 2). Results are very similar for OS and DFS.

Overall survival by clinical stage at 3 years was 100% for stage I, 83% for stage II, 64% for stage IIIa and 40% for stage IIIb. There was a significant difference between clinical stages in DFS (log-rank trend $p < 0.001$), and a significant difference in OS when comparing clinical stages grouped in I–IIIa with IIIB (log-rank $p = 0.001$, Fig. 3). In a univariate analysis, age older than 60, having received full treatment as specified above and dose >45 Gy were all significantly related to OS ($p < 0.05$). The low number of patients precludes further statistical analysis.

4. Discussion

Radio-chemotherapy has been a standard of care for nearly 30 years since Norman Nigro first published his results in 1974.[5] In that article, Nigro showed preliminary data of three patients treated with preoperative combined modality therapy with such promising results that radio-chemotherapy became a primary treatment, leaving surgery to rescue patients who failed treatment.

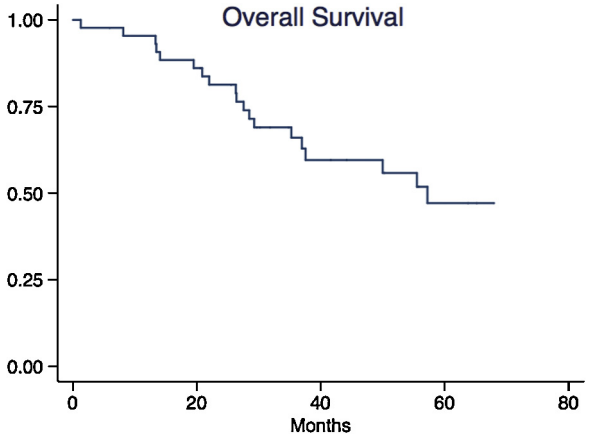

Fig. 2 – Kaplan–Meier curves for overall survival for all patients.

Several trials have compared radio-chemotherapy with radiation alone, consistently showing better outcomes in the combined modality treatment arm. In 1984, Bernard Cummings and colleagues published a retrospective report of 30 patients treated with radio-chemotherapy with 5-fluoracil and mitomycin, and 25 patients treated with radiation alone with a similar radiation technique.[6] Patients were similarly staged and where broadly comparable. Patients received 30 Gy with multiple-beam external radiation to the pelvis including the inguinal nodes, with a dose above 45 Gy to the primary tumor. Most of the treatment failures were local failures, and radio-chemotherapy significantly improved primary relapse free survival and colostomy free survival.

In a large study published in 1996 (ACT I) and updated in 2010 with 13 years of follow-up, 585 patients were randomized to receive radiotherapy with or without chemotherapy.[7] Radiation consisted on 45 Gy to the pelvis with a 15 Gy boost to the primary with a 6-week break in between. Chemotherapy included 5-FU and mitomycin. The combined modality arm had a better 3-year local control (36% vs. 59%), with no difference in overall survival.

Bartelink similarly compared both treatments in 110 patients with locally advanced anal cancer.[8] Also using a 6-week break after 45 Gy of external beam radiotherapy 5-FU and mitomycin were added, with and improved 5-year local control of 68% vs. 50%, colostomy free survival from 40% to 72% and disease free survival from 43% to 61%. Complete responses were also improved from 54% to 80%.

Because of the high incidence of hematological toxicity, several attempts have been made to replace or remove mitomycin from the radio-chemotherapy scheme in anal cancer treatment. Flam and colleagues published RTOG 87-04, a randomized trial comparing radio-chemotherapy with 5-Fu with or without mitomycin in 310 patients.[9] Patients had a biopsy performed 4–6 weeks after treatment. In patients with residual disease, a 9 Gy radiation boost was given to the perineum, inguinal nodes or both. In these patients, another biopsy was performed, and in patients with persistent disease an

abdomino-perineal resection was done 3–4 weeks later. The disease free survival rate increased from 51% with 5-FU and radiation to 73% with radiation combined with 5-FU and mitomycin. The colostomy rate decreased from 22% with radiation and 5-FU to 9% with radiation, 5-FU, and mitomycin.

In 2010 the results of a phase III intergroup trial were reported of 644 patients comparing 5-FU, mitomycin, and radiation to 5-FU, cisplatin, and radiation.[10] The substitution of Cisplatin for mitomycin did not only failed to improve disease-free survival, but colostomy rates were significantly higher in the group randomized to cisplatin. Mitomycin did, however, have greater toxicity than cisplatin. The authors concluded that mitomycin remained the standard.

Early European trials planned a gap in radiation therapy after 45 Gy in order to decrease toxicity while giving a high dose to the primary. Radiation dose has historically been at least 45 Gy even in early stages. Studies that have used higher doses have not shown improved results, but one must note that these studies have used split course radiation, which could be accountable for the lack of benefit of increased dose.[6–8]

Another subject that has not been settled yet, apart from radiation dose, is the need for elective irradiation of inguinal nodes in patients with clinically N0 disease. Two recent studies have shown benefit of prophylactic inguinal radiotherapy. TROG 99.02 evaluated patients with T1–T2, N0 anal carcinoma with no elective radiation of inguinal nodes, treated with radio-chemotherapy with 5-FU and mitomycin, with a 44-month follow-up.[11] Inguinal failure occurred in 22.5% of patients, and was isolated in only 12.5%. A retrospective French study analyzed 208 patients, mostly with T1–T3 tumors.[12] Of 181 patients with uninvolved nodes at presentation, 75 received prophylactic radiation to inguinal nodes and 106 did not. Even though patients who received elective radiation of inguinal nodes had on average larger tumors, they did significantly better in terms of inguinal recurrence (2% vs. 16%). Specifically for T1–T2 tumors, the 5-year inguinal recurrence risk when omitting elective radiation of the inguinal nodes was estimated to be as high as 10%. Considering the above data, prophylactic radiotherapy of the inguinal nodes is recommended in T3–T4 tumors and should be considered in patients with earlier stages (T1–T2). Because there may be wide variations in the depth of inguinal nodes, axial imaging should be used to determine the best technique and proper prescription for prophylactic inguinal node radiation.

Results of treatment in our cohort of patients, which were largely HIV negative, are fairly comparable to published clinical trials. Interesting findings were that age older than 60, having received full treatment and dose >45 Gy were all significantly related to OS ($p < 0.05$). Standard of care treatment, with the specific characteristics discussed above, has been an effective treatment modality at the IRAM in the management of anal canal cancer. Treatment modifications or intensifications for patients presenting with stage IIIb disease, where results are dismal, need to be explored.

Conflict of interest

None declared.

Financial disclosure

None declared.

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