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THE EFFICACY OF RADIOTHERAPY IN PERIANAL INTRAEPITHELIAL NEOPLASIA GRADE 3

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Abstract – *Objective:* To determine the efficacy of radiotherapy in the local control of Perianal Intraepithelial Neoplasia Grade 3 at a single institution.

Patients and Methods: *This retrospective case series consists of 30 patients treated with local radiotherapy (RT) at the British Columbia Cancer Agency between 1997 and 2017. Chart review was performed to abstract data on patient and treatment characteristics. Outcomes evaluated were local control and survival.*

Results: *Of the 30 patients, 5 had local failure, 3 as recurrent* in-situ *disease, and 2 as invasive disease. Only 1 recurrence occurred before 5 years. Radiotherapy doses ranged from 42.5 – 60 Gy. The actuarial 5 and 10 year local control rates were 96% and 51%, respectively. 3 patients had a treatment break due to acute RT reaction. Of 6 recorded deaths, none was due to anal disease.*

Conclusions: *Moderate dose local RT is associated with excellent local control of Perianal Intraepithelial Neoplasia Grade 3 with minimal acute toxicity.*

KEYWORDS: Perianal intraepithelial neoplasia, Radiotherapy, Local control.

INTRODUCTION

Perianal Intraepithelial Neoplasia grade 3 (PAIN3) is a dysplastic lesion of the perianal skin associated with HPV infection[1]. PAIN3 is synonymous with squamous carcinoma-*in-situ* of the perianal skin, Bowen's Disease, perianal dysplasia, and more recently High Grade Squamous Intraepithelial Lesion as defined by the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology[2]. PAIN3 is known to progress and transform to invasive squamous carcinoma at rates of approximately 1-2% per year[3-5]. Conversely, PAIN3 may regress spontaneously at a rate of 23.5% per year in recent observational studies[6]. In recognition of the significant risk of local recurrence and potential progression to invasive squamous carcinoma, the American Society of Colon and Rectal Surgeons recommends that patients with PAIN3 be followed regularly with history, physical and a discussion of screening options, despite a lack of strong evidence, inconvenience to the patient, and health care cost[7].

Multiple treatment modalities have demonstrated efficacy in controlling PAIN3, including surgery[8,9], local ablative procedures[10-17], and various topical agents[18-22]. However, complete response rates are widely variable, and local recurrence rates for most modalities are sufficiently high, with risk of progression to invasive disease necessitating ongoing surveillance and repeated procedures.

Radiotherapy has proven utility in eradicating intraepithelial neoplasia in other anatomic locations, particularly glottis of the larynx where it is considered standard therapy[23-27] but also in skin sites[28-31], but there is minimal published literature

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regarding its efficacy in the perianal skin region, where the biology may potentially differ, particularly on the basis of HPV association. In the perianal or anal canal site, there are only anecdotal case reports[32,33] or small case series[34,35] demonstrating the efficacy of radiotherapy to treat PAIN3 or Anal Intraepithelial Neoplasia grade 3 (AIN3). The largest reported series of 9 patients suggests 100% local control[34]. The other case series involving 3 patients also report 100% local control[35]. One of the two case reports documents local recurrence 2 years following treatment with primary chemoradiotherapy[33].

Multiple national bodies have published guidelines for the treatment of PAIN3, including the American Society of Colon and Rectal Surgeons both in 2012 and 2018[36,37], the Association of Coloproctology of Great Britain and Ireland[38], and the Italian Society of Colorectal Surgery[39]. There is little consensus amongst these recommendations other than the lack of discussion of localized radiotherapy as a valid treatment option, perhaps reflecting the current lack of published literature.

Radiotherapy for PAIN3 has been routinely utilized for at least 20 years at the British Columbia Cancer Agency with anecdotal evidence of good local control with moderate doses.

This study evaluates the delivery, dose and fractionation of radiotherapy used in PAIN3 and assesses recurrence patterns and survival outcomes after treatment.

PATIENTS AND METHODS

Patients

A retrospective case review was performed of all patients aged ≥19 with the diagnosis of squamous carcinoma-*in-situ* of the perianal skin, treated with radiotherapy at the BC Cancer Agency between 1997 and 2017. Patients with an invasive component on the biopsy were included if the invasive component was minimal and had been excised with at least 1 mm margin clearance. Those patients with likely clinical invasive disease remaining, and those with coexisting vulvar squamous carcinoma-*in-situ* were excluded.

Methods

Data abstracted included age at diagnosis, gender, date of diagnosis, tumour location (perianal skin only, anal canal only or both), clinical stage (Tis only, or Tis with microinvasion excised with clear margins), surgical date, surgery type (incisional biopsy, excisional biopsy, or attempted wide local excision), principal histology, radiotherapy characteristics (start and completion dates, technique, duration, presence of treatment delays, toxicity causing delays, dose and fractionation, date of last follow-up, presence of local recurrence, type of recurrence (*in-situ vs.* invasive), and date of death.

Ethical Committee

Research Ethics approval was obtained from the University of British Columbia. As this was a retrospective review of anonymized data, informed consent was not required.

Statistical analysis

Descriptive statistics were utilized to describe the cohort. Local recurrence rates were estimated using Kaplan-Meier statistics. Clinical and pathologic factors associated with recurrence were examined.

RESULTS

31 patients were identified who met the inclusion criteria. 1 patient was excluded from analysis due to difficulty in retrieving the patient's records.

Of the 30 evaluable patients (Table 1), the mean age was 57.4 years (range 35-79), 60% female. 26 patients had disease confined to the perianal region without anal canal involvement, 1 patient had anal canal only involvement, and 3 patients had disease involving both perianal skin and anal canal. 19 patients had documented PAIN3 only, while 11 had an invasive component seen on the biopsy, although all of these patients had demon-

TABLE 1. Patient Characteristics.

Characteristics	*Patients (n=30) N (%)*
Mean age, years	57.4 (35-79)
Sex	
Male	12 (40%)
Female	18 (60%)
Tumor Location	
Perianal skin only	25 (83.3%)
Anal canal only	1 (3.3%)
Perianal skin and anal canal	4 (13.3%)
Surgical Intervention	
Incisional biopsy	10 (33.3%)
Excisional biopsy	18 (60%)
Attempted wide local excision	2 (6.7%)

TABLE 2. Radiotherapy Characteristics

Radiotherapy Characteristics	*Patients (n=30) N (%)*
Radiotherapy technique	
Direct electrons	11 (36.7%)
3D conformal therapy	18 (60%)
Intensity modulated radiotherapy	1 (3.3%)
Treatment break	
None	24 (80%)
Yes	6 (20%)
Planned	1
Unplanned	5 (range from 1 day to 21 days)
Treatment early cessation	
None	28 (93.3%)
Yes	2 (6.7%)
Radiotherapy Median Dose, Gray (range)	50 (42.5 – 60)
Radiotherapy Mean number of fractions (range)	20 (15 – 30)

strated pathological clear margins of at least 1 mm and no evidence on examination or imaging of residual invasive disease. Surgical procedure prior to radiotherapy included incisional biopsy in 10 patients, excisional biopsy in 18 patients, and attempted wide local excision in 2 patients. All of these patients had pathological evidence of PAIN3 at the margin of the specimen.

Radiotherapy characteristics for the cohort (Table 2) consisted of a single electron field for 11 patients, 3D conformal radiotherapy either as a 3-field or 4-field technique in 18, and 1 patient receiving intensity modulated radiotherapy. The doses received ranged from 42.5 Gy to 60 Gy, although the minimum prescription was 45 Gy. The median dose prescribed and delivered was 50 Gy, in 20 or 25 fractions. 6 patients had treatment breaks: one was a planned split course, 2 were due to machine breakdown of 1 day each, and 3 were due to severe acute dermatitis, including 3, 4, and 21 days delay. Two patients had 1 and 3 fractions of radiotherapy omitted due to acute perianal skin toxicity.

TABLE 3. Recurrence and survival outcomes

Characteristics	*Patients (n=30) N (%)*
Recurrence rate, 5 years	4%
Recurrence rate, 10 years	49%
Recurrence type	
AIN3 only	3
Squamous carcinoma	2
Cause of Death	
Metastatic Lung Cancer	4
Multiple Myeloma	1
Unknown, but no evidence of AIN3	1

Median follow up of the cohort was 38 months (range 3-164 months). Recurrence and survival outcomes are summarized in Table 3. The 5-year KM local control was estimated at 96% with one case of local recurrence at 20 months (Figure 1). This patient had tolerated the radiotherapy poorly and only received 42.5 Gy in 17 fractions, with treatment discontinued after 17 of 20 planned fractions. 4 additional recurrences were noted after 5 years of follow up, including a patient recurring after more than 13 years from radiation treatment completion date. Of the 5 recurrences, 3 were recurrent PAIN3, and 2 were invasive squamous cell carcinoma. The 2 patients recurring with invasive disease, and one of the patients with recurrent PAIN3 were treated with salvage abdominal perineal resection. One patient who recurred with PAIN3 after 5 years was offered topical fluorouracil and salvage abdominal perineal resection but declined both options. This patient remains on follow-up with persistent low volume PAIN3. One patient who recurred with PAIN3 was not treated for salvage due to having synchronous end-stage multiple myeloma.

Of the 6 recorded deaths, 4 were due to metastatic lung cancer, 1 was due to multiple myeloma, and 1 was due to unknown causes, but unrelated to anal disease.

No significant association between recurrence risk was observed with age, gender, site of disease, coexistence of invasive disease, type of surgery, radiotherapy technique, or radiotherapy delay (all $p>0.05$). There was a trend between lower radiotherapy dose and recurrence, with 3 of 8 patients receiving less than the median 50 Gy experiencing a recurrence, and 2 of 22 patients receiving the median or greater dose, $p=0.10$.

In the analysis of overall survival, the only significant factor was age of diagnosis, with all patients who died on observation having been older than the median age of 56.5 years.

DISCUSSION

The natural history of PAIN3 includes both regression and conversion to invasive disease. Older observational studies have suggested that the conversion rate was relatively low, although more recent studies have reported rates of 1-3% per year[3-5]. Current treatment recommendations typically include ongoing close surveillance with high resolution anoscopy and local ablative procedures such as cryotherapy, curettage and cautery, infrared coagulation, radiofrequency ablation, photodynamic therapy, electrocautery, argon plasma coagulation or topical agents such as 5 fluorouracil,

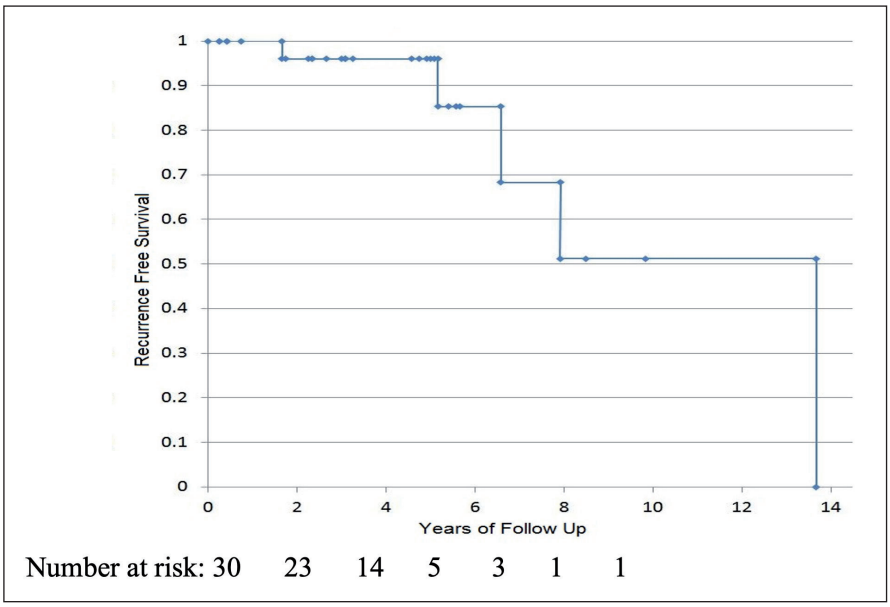

Fig. 1. Recurrence Free Survival.

imiquimod, trichloroacetic acid or cidofovir[7,37,38]. A randomized controlled trial evaluating topical imiquamod, topical fluorouracil, or electrocautery demonstrated recurrence rates of 71%, 58% and 68% at 72 weeks, respectively (18). Previous standard of care of wide local excision with skin grafting is no longer recommended on the basis of progressive anal stenosis, and incontinence, especially with repeated procedures and circumferential lesions. Due to high recurrence rates, and risk of progression to invasive disease, The American Society of Colon And Rectal Surgeons, the Association of Coloproctology of Great Britain and Ireland and the Italian Society of Colo-rectal surgery all recommend close surveillance including potential screening (37-39). Only the Italian Society mentions radiotherapy as a therapeutic option.

Interestingly, despite the proven utility of local radiotherapy in squamous carcinoma-*in-situ* in larynx and skin, there is a paucity of literature with respect to utilization for PAIN3 or AIN3.

A case series of 44 cases from the Princess Margaret Hospital examined the utility of radiation therapy in all anatomic sites of Bowen's Disease of the skin included 3 lesions involving the perianal skin. Multiple dose fractionation schedules were utilized but were fairly low compared to today's standards. 25 Gy in 10 fractions, for example, was a common treatment prescription, given with a direct orthovoltage field[35]. 42 complete responses were documented, with 3 local recurrences, none of which included the perianal skin. A case series of early anal cancer from France included 9 patients with PAIN3 treated at multiple different institutions with various doses, fractionation and radiotherapy modalities including brachytherapy, demonstrated local control in all patients with a median follow-up of 66 months[34].

The current report is the largest case series of PAIN3 treated with local radiotherapy, with relatively homogenous technique of external beam radiotherapy, with fairly standard dose and fractionation, all treated at the same institution. The complete response rate of 100% and actuarial 5 year local control rate of 96% appear to be more favorable than other modalities reported, and consistent with published case series and case reports. The only patient with disease recurrence prior to 5 years tolerated treatment poorly and received the lowest dose of the cohort due to early termination of radiotherapy.

As it was standard institutional practice to discharge patients after 2 to 3 years of follow-up, the median follow-up of 38 months for this cohort is somewhat incomplete, but much longer than most reported series. The recurrence rate as an invasive carcinoma of 0% at 5 years compares favorably with the natural history reported risk of 1-2% per year. Although we do not perform routine follow-up beyond 5 years, it is highly likely that most local recurrences would be re-referred for further consultation. The observation that 4 of the local recurrences occurred after 5 years, and 1 after 13 years, suggests that patients are more at risk for a late, rather than early local recurrence. The possibility also exists that these patients have recurred as *de novo* primary lesions as opposed to true local failures, as might be expected from a field cancerization effect.

The limitations of this study include its retrospective design, with inherent biases in patient and treatment selection. The study also lacked data on

functional and quality of life outcomes. However, it would be anticipated that with perianal skin involvement only, radiotherapy fields would treat very small volumes, and expected long-term toxicity would likely be low. Acknowledging these limitations, the current analysis offers the largest available series of patients with PAIN3 treated with radiation using relatively modern techniques at a provincial institution.

CONCLUSIONS

Moderate dose local RT is associated with high complete response rates and very low 5-year local recurrence rates in patients with PAIN3. These observations support the suggestion that localized radiotherapy to small volumes of perianal skin is a reasonable treatment option for patients with high risk for recurrence and / or progression to invasive carcinoma.

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Howard Joe led the conception and design of the study, acquisition of data, analysis and interpretation of data and drafting the article. Tracy Mitchell and Pauline Truong contributed in study design, acquisition of data, interpretation of data and reviewing the article with critical revisions related to relevant intellectual content of the manuscript. All 3 authors provided final approval of the version of the article to be published.

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The authors declare that they have no conflict of interest to disclose.

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