

Management of small (T1–T2) anal margin squamous cell carcinoma: clinical outcomes following local excision alone

Roji, A. M.; Namiq, K. F.; Radley, S.; Ismail, T.; Hejmadi, R.; Taniere, P.; Geh, J. I.

DOI:

[10.1111/codi.16562](https://doi.org/10.1111/codi.16562)

License:

Creative Commons: Attribution-NonCommercial (CC BY-NC)

Document Version

Publisher's PDF, also known as Version of record

Citation for published version (Harvard):

Roji, AM, Namiq, KF, Radley, S, Ismail, T, Hejmadi, R, Taniere, P & Geh, JI 2023, 'Management of small (T1–T2) anal margin squamous cell carcinoma: clinical outcomes following local excision alone', *Colorectal Disease*, vol. 25, no. 7, pp. 1403-1413. <https://doi.org/10.1111/codi.16562>

[Link to publication on Research at Birmingham portal](#)

General rights

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

- Users may freely distribute the URL that is used to identify this publication.
- Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
- User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
- Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

Take down policy

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.



European Colorectal Congress

3 – 6 December 2023, St.Gallen, Switzerland

OVERVIEW

Sun, 3 Dec 2023

MASTERCLASS

PROCTOLOGY DAY

ROBOTIC COURSE

DAVOSCOURSE@ECC

SCIENTIFIC PROGRAMME

Mon, 4 Dec – Wed, 6 Dec 2023

DIVERTICULAR DISEASE

Gut microbiome and surgery

Phil Quirke, Leeds, UK

Diet in diverticular disease

Pamela Buchwald, Lund, SE

Decision making in the management of acute complicated Diverticulitis beyond the guidelines

Seraina Faes, Zurich, CH

Diverticular Abscess – Always drainage or who benefits from Surgery?

Johannes Schultz, Oslo, NO

Perforated Diverticulitis: Damage Control, Hartmann's Procedure, Primary Anastomosis, Diverting Loop

Reinhold Kafka-Ritsch, Innsbruck, AT

When to avoid protective stoma in colorectal surgery

Antonino Spinelli, Milano, IT

ENDOMETRIOSIS

Endometriosis – what is the role of the abdominal surgeon

Tuynman Juriaan, Amsterdam, NL

Challenges in Surgery of Endometriosis – always interdisciplinary?

Peter Oppelt, Linz, AT; Andreas Shamiyeh, Linz, AT

A gaze in the crystal ball: Where is the role of virtual reality and artificial Intelligence in colorectal surgery

Müller Beat, Basel, CH

MALIGNANT COLORECTAL DISEASE

Cytoreductive Surgery and Intraperitoneal Chemotherapy – facts and hopes

Michel Adamina, Winterthur, CH

Metastatic Colorectal Cancer – surgical approaches and limits

Jürgen Weitz, Dresden, DE

Extended lymph node dissection for rectal cancer, is it still under debate?

Miranda Kusters, Amsterdam, NL

Organ preservation functional outcome in rectal cancer treatment – in line with patient's needs? (Robot – laparoscopic – open surgery?)

Hans de Wilt, Nijmegen, NL

ROBOTICS

Advances in Robotic Surgery and what we learnt so far

Parvaiz Amjad, Portsmouth, UK

Challenging the market: Robotic (assistant) Devices and how to choose wisely (Da Vinci – Hugo Ras – Distalmotion ua)

Khan Jim, London, UK

TAMIS - Robotic Transanal Surgery, does it make it easier?

Knol Joep, Genk, BE

Live Surgery – Contonal Hospital of St.Gallen

Walter Brunner, St.Gallen, CH;
Salvadore Conde Morales, Sevilla, ES;
Friedrich Herbst, Vienna, AUT;
Amjad Parvaiz, Portsmouth, UK

Video Session

Lars Pahlmann Lecture

Markus Büchler, Lisboa, PRT

Honorary Lecture

Bill Heald, Lisboa, PRT

Information & Registration www.colorectalsurgery.eu



ORIGINAL ARTICLE

Management of small (T1–T2) anal margin squamous cell carcinoma: clinical outcomes following local excision alone

A. M. Roji¹ | K. F. Namiq^{1,2} | S. Radley¹ | T. Ismail¹ | R. Hejmadi¹ | P. Taniere¹ | J. I. Geh^{1,2}

¹Queen Elizabeth Hospital, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK

²School of Cancer Sciences, University of Birmingham, Birmingham, UK

Correspondence

J. I. Geh, The Cancer Centre at the Queen Elizabeth Hospital, Edgbaston, Birmingham B15 2TH, UK.
Email: ian.geh@uhb.nhs.uk

Funding information

The Higher Committee for Education Development in Iraq

Abstract

Aim: Squamous cell carcinomas of the anus are normally treated with synchronous chemoradiotherapy (CRT). Small, localized anal margin tumours may be adequately treated by local excision (LE) alone. This study aims to investigate the outcomes of patients with anal margin tumours treated with LE alone, reserving the use of CRT for salvage on local recurrence (LR).

Methods: Patients with small, localized (stage I/IIA) anal margin tumours treated by LE from October 1999 to September 2018 were identified. The effect of tumour size and resection margin on LR risk was analysed. Outcomes of overall survival and disease-free survival were measured.

Results: Fifty-five patients with anal margin tumours were identified. Overall 5-year LR, overall survival and disease-free survival rates were 8%, 86% and 82% respectively. Of the seven LRs, five were successfully salvaged with CRT with no further recurrence and two were not fit for CRT. Resection margins in non-fragmented tumours and tumour size did not significantly influence LR risk.

Conclusions: Most small, localized anal margin tumours can be adequately treated by LE alone with low LR rates. Most patients who developed LR were salvaged using CRT, with no cancer-related deaths reported.

KEYWORDS

anal cancer, clinical outcomes, local excision, local recurrence, squamous cell carcinoma of anus

INTRODUCTION

Squamous cell carcinoma (SCC) of the anus is uncommon and can arise from the anal canal or the anal margin. It accounts for approximately 4% of lower gastrointestinal tumours, but its incidence is rising [1, 2]. The disease often remains localized to the primary site and regional lymph nodes, with only 5%–8% having systemic spread at presentation. Five-year overall survival is around 70%–80% [3, 4]. Human papillomavirus infection (types 16 and 18) is the main risk factor for anal cancer [5].

Most patients receive treatment with curative intent using synchronous chemoradiotherapy (CRT) [3], aiming to achieve locoregional control, preserve anal sphincter function and provide good long-term quality of life [4]. Abdominoperineal resection is usually reserved as salvage for refractory or recurrent disease. However, it is recognized that patients with small anal tumours are probably overtreated with CRT, in terms of radiation dose and volume, but there is a scarcity of evidence for treatment de-escalation in this group of patients. Hatfield et al. [6] previously reported the use of

Abbreviations: CRT, chemoradiotherapy; DFS, disease-free survival; HIV, human immunodeficiency virus; HPV, human papillomavirus; LE, local excision; OS, overall survival; RM, resection margin.

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial](https://creativecommons.org/licenses/by-nc/4.0/) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2023 The Authors. *Colorectal Disease* published by John Wiley & Sons Ltd on behalf of Association of Coloproctology of Great Britain and Ireland.

a low dose, reduced volume, involved field CRT in small T1–T2 anal tumours showing good clinical outcomes. The current UK National Cancer Research Institute (NCRI) PLATO ACT4 trial is evaluating the effectiveness of reducing the radiation dose in patients with T1 and small (<4 cm) T2 tumours [7], in view of the potential overtreatment of small anal cancers receiving the same radiation dose as significantly larger tumours.

Small, localized anal margin tumours may be adequately treated with local excision (LE) alone without the need for CRT and its potential late toxicity risks [8]. However, there are few published trials and series which quantify the risk of local recurrence (LR) in patients treated by LE alone for anal margin tumours [9]. There are no data correlating LR risk with resection margins (RMs) to determine the minimal margin necessary to achieve local disease control. Due to the paucity of such evidence, published guidelines recommend variable histological margins ranging from 1 to 10 mm [4, 10–12]. This leads to variation in clinical practice and patients are often offered adjuvant CRT following LE, either routinely or if perceived to be at higher risk of recurrence. Where feasible, the use of a wider excision of the tumour site may be another option to be considered.

The Queen Elizabeth Hospital Birmingham (QEHB) has been the regional anal cancer centre since 2004, receiving referrals from five surrounding hospital colorectal cancer multidisciplinary teams (MDTs). At the anal cancer MDT, the histology from biopsy and staging imaging is reviewed, and patients are assessed for further treatment. In patients who have had a complete macroscopic and microscopic LE of an anal margin tumour, further treatment may not be required. For these patients, histology review is aimed at confirming the diagnosis of invasive SCC and to assess the completeness (margins) of excision. Extrapolated from rectal cancer data, a measured tumour RM of >1 mm is generally regarded as clear (R0 resection) and a margin ≤1 mm is regarded as involved (R1 resection) [10, 13, 14]. In addition, the largest diameter of the invasive component of the SCC is measured (to determine T stage), together with the presence or absence of adjacent anal intraepithelial neoplasia (AIN) and its grade.

Another UK NCRI PLATO trial, ACT3, is currently evaluating the role of observation or adjuvant reduced dose CRT in small, locally excised, anal margin tumours depending on the margin of excision [7]. Here, our study aims to contribute to the evidence base by documenting the outcomes of patients with localized (Stage I/II) anal margin tumours treated by LE only, with or without salvage CRT on LR, with emphasis on defining risk factors for LR.

METHODS

Patients

All patients referred to the regional anal cancer MDT at the QEHB are prospectively recorded on an anal cancer database. From this resource, we retrospectively reviewed data of patients with locally excised anal margin SCC referred between October 1999 and August

What does this paper add to the literature?

We report the recurrence rate of patients with small anal margin tumours treated by surgical excision alone and correlate this with the histopathology. There are only a few other large published series on this topic. We found that local recurrence rates are generally low, apart from in patients with fragmented excisions.

2018. Demographic, clinical and histopathological details were collected via systematic review of patient records within the electronic patient database. Patients treated with adjuvant CRT were not included in the analysis. This study was approved by our local audit management system (reference number CARMS-13441).

Definition of anal tumours

Anal margin tumours were defined as those where the tumour itself, or the scar excision site, was directly visible or with digital effacement of the anus, or within a radius of 5 cm from the anal orifice. By contrast, anal canal tumours were defined as those where the tumour itself, or the scar excision site, was only visible on proctoscopy. Some tumours involved both the anal margin and anal canal; these were classified as where the greatest proportion of the lesion lay. This study looked only at anal margin tumours, as defined above.

Staging

Tumour classification and staging followed the 7th edition of the American Joint Committee on Cancer TNM staging. T1 refers to tumour size ≤2 cm; T2 >2 cm and ≤5 cm; T3 >5 cm; T4 invasion of adjacent organs. N1 refers to perirectal lymph node involvement; N2 unilateral internal iliac and/or inguinal lymph node involvement; N3 mesorectal and inguinal lymph nodes and/or bilateral internal iliac and/or inguinal lymph node involvement. M1 refers to the presence of distant metastases. Staging information was gathered from post-surgical histology and, if undertaken, pre-treatment/subsequent staging imaging with CT of the thorax, abdomen and pelvis and/or MR imaging of the pelvis.

General management and surveillance of locally excised anal margin tumours

Following LE, the following policy was agreed and adopted by our anal cancer MDT. For patients with R0 resection, no further treatment was recommended, and routine follow-up consisted of clinical examination at 3–4-month intervals for the first 18–24 months, then every 6 months until 60 months. After 60 months, patients were discharged from follow-up. If the RM was R1 or uncertain,

provided that the excision scar was clear of the anal sphincter muscles, patients were considered for further LE of the scar/tumour bed with or without peri-anal mapping biopsies by the anal cancer MDT surgeon(s), looking for residual disease and multifocal AIN. If no residual invasive SCC was found histologically, the RM was considered adequate (>1 mm) and no further treatment was recommended. Routine follow-up would be as for R0 resected tumours. If residual invasive SCC was present, the RM of the subsequent excision was then assessed. If this was >1 mm, routine follow-up was recommended, but if this remained involved (≤ 1 mm) the options of either adjuvant CRT or close surveillance keeping CRT as salvage treatment on recurrence were discussed with the patient.

Data analysis

Data were presented as frequencies, means and median with ranges. The effect of tumour size and RM on LR risk was analysed. Other outcomes measured included overall survival and disease-free survival. Kaplan–Meier plots were used to display the recurrence rates and survival curves. Univariate comparisons of outcomes were conducted using Cox regression analysis. A *P* value of <0.05 was considered statistically significant. Data were analysed using JAMOVI (version 2.0) statistical software.

RESULTS

Baseline characteristics

During the 18-year period studied, 529 referrals were seen at QEHB. Of these, a total of 57 (10.8%) patients with anal margin SCC were identified to have had LE. Of these, two patients received adjuvant CRT and were excluded from this analysis (Figure 1). Baseline characteristics of the remaining 55 patients are summarized in Table 1. Patients had a median age of 52 years (range 30–86 years) and presented with median tumour size of 1.5 cm (range <0.1 –4.7 cm) diameter. Three patients (5.5%) had basaloid sub-type, eight female patients (14.5%) had previous treatment for human-papillomavirus-related gynaecological cancers or pre-malignant conditions (cervical intraepithelial neoplasia, vulvar intraepithelial neoplasia, vaginal intraepithelial neoplasia), and two patients (3.6%) were known to be human immunodeficiency virus (HIV) positive prior to diagnosis.

Surgical excision and histology

All 55 patients with anal margin tumours were treated by LE alone; 47 (85.5%) had T1 tumours and eight (14.5%) had T2 tumours (Table 1). An R0 resection (RM >1 mm) was achieved on initial LE in 21 patients and an R1 resection (RM ≤ 1 mm) in 26 patients. Of the 26

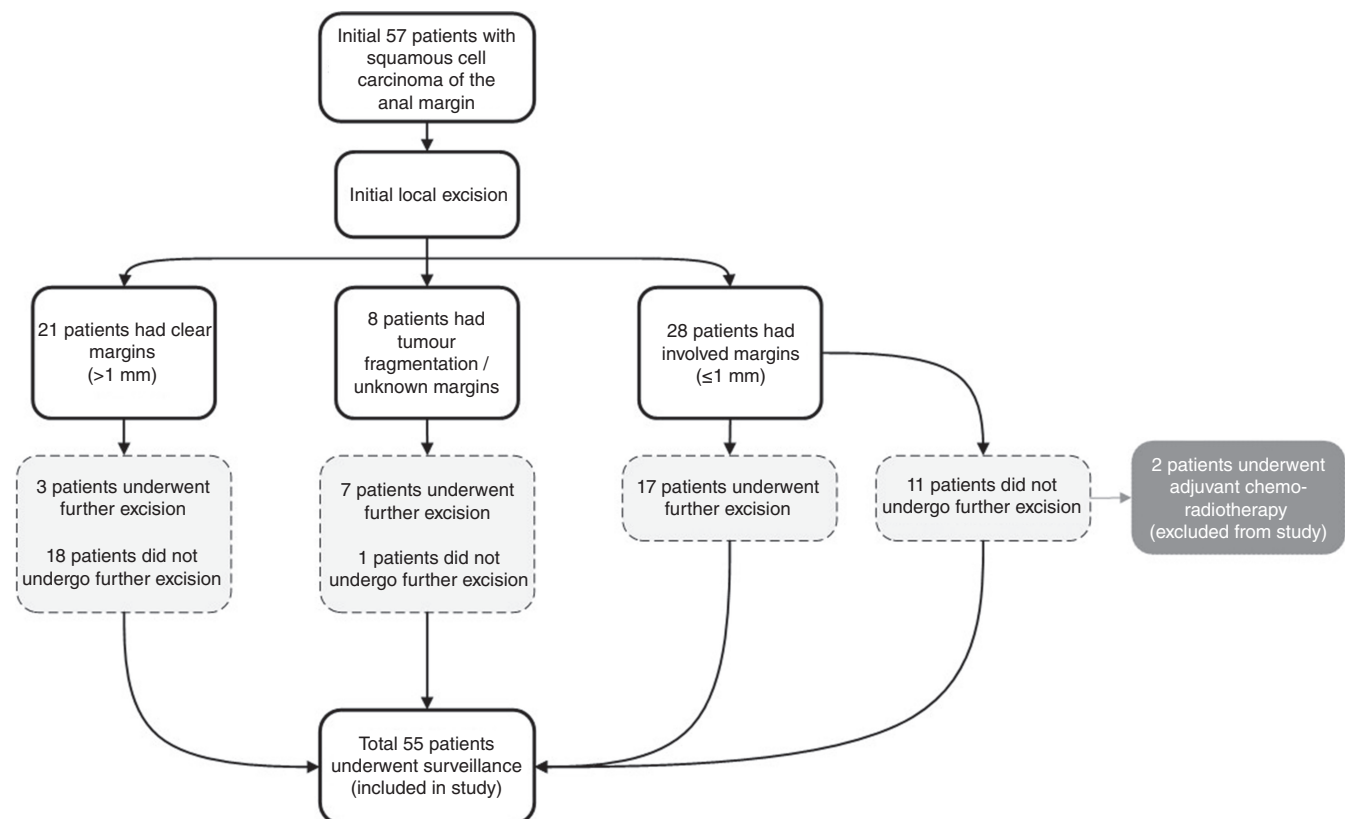


FIGURE 1 Flowchart of patients with locally excised squamous cell carcinoma of the anal margin who were selected for inclusion in the study.

patients with an involved RM, 17 patients had further LE; no residual tumour/AIN was found in 12 patients, with five patients having residual AIN 2–3. As such, 38 of these patients (69.1%) had a clear final RM. The remaining nine patients (16.4%) did not undergo further LE. In the other eight patients (14.5%), the RM was unknown—either not

stated ($n=3$) or not assessable due to tumour fragmentation ($n=5$). Of these, seven patients had further LE with clear margins (>1 mm) (Table 2), with residual SCC found in three patients and AIN 2–3 in four patients.

TABLE 1 Summary of patient demographics and characteristics of tumours for patients with locally excised squamous cell carcinoma of the anal margin.

Characteristics	Anal margin
Number of patients	55
Median follow-up of live patients (range)	58.6 months (4–229 months)
Age (years)	
Median	52
Range	30–86
Sex (%)	
Male	23 (41.8%)
Female	32 (58.2%)
Male/female ratio	1:1.4
Previous history of HPV-related gynaecological cancers or premalignant conditions	8/32 (14.5%)
Known HIV history (%)	2 (3.6%)
Basaloid sub-type	3 (5.5%)
Primary tumour (T)	
Median diameter (cm), range	1.5 (<1.0 to 4.7)
T1 (tumour ≤ 2 cm)	47 (85.5%)
T ≤ 1 cm	30 (54.5%)
T > 1 cm	17 (30.9%)
T2 (tumour > 2 cm but ≤ 5 cm)	8 (14.5%)
Final resection margins	
Clear margins (RM > 1 mm)	38 (69.1%)
Involved margins (RM ≤ 1 mm)	9 (16.4%)
Initial tumour fragmentation/unknown margins	8 (14.5%)

Staging

Thirty-four patients underwent staging imaging with CT thorax, abdomen and pelvis and/or MRI pelvis as part of the diagnostic workup, whether pre- or post-LE. No extra-pelvic disease or distant metastases was noted on any of the staging imaging conducted. Twenty-one patients did not have pre- or post-LE staging imaging. However, no significant correlation with LR was seen with patients who did or did not have staging imaging as part of the diagnostic workup.

Overall survival and disease-free survival

After a median follow-up interval of 58.6 months (range 4–229 months; 85.7% for over 24 months), the 3- and 5-year overall survival in the anal margin tumour group was 89% and 86% and disease-free survival was 82% and 82%, respectively (Figures 2 and 3, Table 4). Six patients had died: two from metastatic disease and the remaining four from unrelated causes.

Local recurrences and distant metastases

Seven (12.7%) patients developed LR (in the absence of lymph node or distant metastases) with a median time of 23.5 months (range 12.9–125.5 months). Two of these patients recurred beyond 100 months; therefore these are likely to represent new primaries rather than genuine LR. The remaining five patients developed LR within 40 months of initial LE. The maximum diameter of LRs seen ranged from 0.5 to 4 cm. Of these seven patients, five were successfully salvaged with CRT and remain alive with

Initial resection margins		Re-excision		Clear final resection margins?		Local recurrence (%)	
		Yes	No	Yes	No	Yes	No
Clear initial margins (> 1 mm)	21	Yes	3	Yes	17	0/17 (0%)	2/21 (10%)
		No	18	No	9	1/9 (11%)	
Involved initial margins (< 1 mm)	26	Yes	17	Yes	17	0/17 (0%)	5/26 (19%)
		No	9	No	9	1/9 (11%)	
Fragmented/unknown margins	8	Yes	7	Yes	7	3/7 (43%)	1/8 (12.5%)
		No	1	No	1	1/1 (100%)	
All patients	55			Yes	45	5/45 (11%)	10/55 (18.2%)
				No	10	2/10 (20%)	

TABLE 2 Local recurrence according to the resection margin in patients with locally excised squamous cell carcinoma of the anal margin.

FIGURE 2 Kaplan–Meier curves for overall survival for patients with locally excised squamous cell carcinoma of the anal margin.

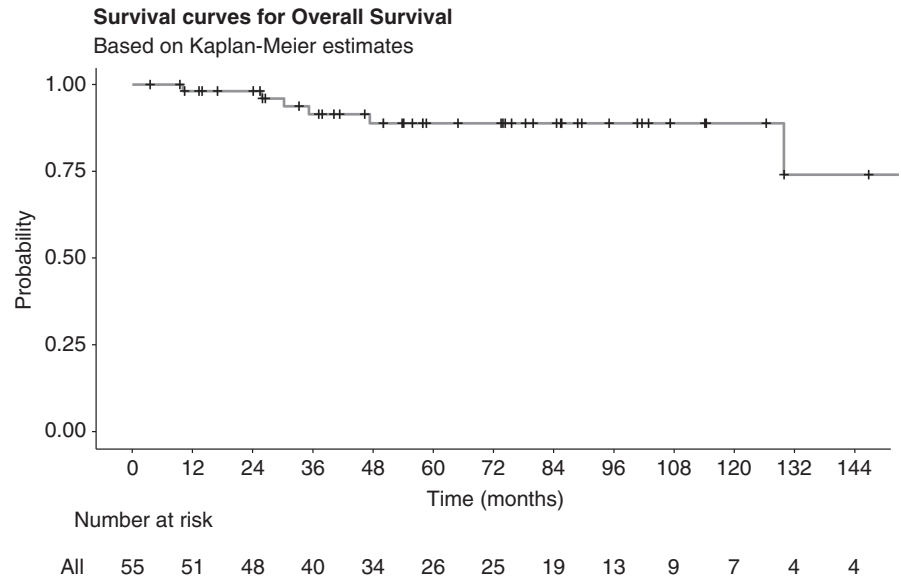
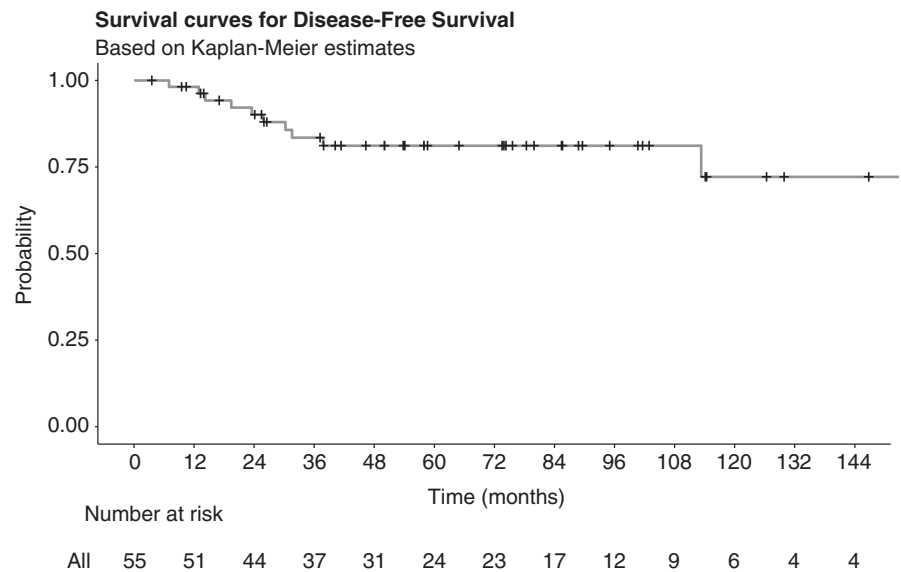


FIGURE 3 Kaplan–Meier curves for disease-free survival for patients with locally excised squamous cell carcinoma of the anal margin.



no further recurrence. Of the remaining two patients, one was not fit to receive CRT whilst the other did not complete CRT due to increased toxicity (Table 3). Overall, the 3- and 5-year risk of LR was 8%.

Two (3.6%) patients developed multi-site metastases (both had inguinal lymph nodes and lung metastases) in the absence of LR (Table 3). They were treated with palliative intent.

In the 38 patients with a clear final RM on initial or further LE (excluding patients with unknown initial RM/tumour fragmentation), two patients developed LR. In the nine patients with an involved RM (no further LE), one patient developed LR after more than 10 years' follow-up. There was no detectable increase in LR seen between patients with involved RM compared to those with clear final RM (hazard ratio 3.43; 95% CI 0.31–38.06, $P=0.315$). The remaining eight patients with unknown initial RM/tumour fragmentation had a higher incidence

of LR in comparison, with four patients developing LR (hazard ratio 20.95; 95% CI 1.96–223.71, $P=0.012$) (Table 2, Figure 4). Further LE after fragmented resection did not seem to influence LR risk.

The size of anal margin tumours did not affect the LR risk, as no detectable increase in LR was seen when comparing patients with T1 and T2 tumours ($P=0.59$) (Figure 5).

Long-term morbidity

No patient in this study reported symptoms of severe faecal incontinence. No patients required stoma formation, either temporary defunctioning or permanent. All patients with LR who were fit for CRT were rendered disease-free following further treatment and no patients required salvage abdominoperineal resection.

TABLE 3 Characteristics, further treatments and outcomes for patients with locally excised squamous cell carcinoma of the anal margin who experienced disease recurrence.

Patient age (years) and gender (M/F)	Size of tumour (cm)	Initial margins	Clear final margins?	Time to recurrence (months)
86F	4.5	Clear	Yes	Local recurrence at 19.4 months
49M	2.9	Involved, no further excision	No	Local recurrence at 125.5 months
58F	<1.0	Fragmented, further excision	Yes	Local recurrence at 113.3 months
81F	1.1	Fragmented, no further excision	No	Local recurrence at 14.2 months
60F	2.0	Fragmented, further excision	Yes	Local recurrence at 12.9 months
73F	<1.0	Fragmented, further excision	Yes	Local recurrence at 37.8 months
72M	<1.0	Clear	Yes	Local recurrence at 23.5 months
67M	1.0	Involved, further excision	Yes	Regional lymph nodes and distant metastases at 31.5 months
64F	2.0	Involved, further excision	Yes	Regional lymph nodes and distant metastases at 7 months

Abbreviations: 5FU, fluorouracil; MMC, mitomycin-C.

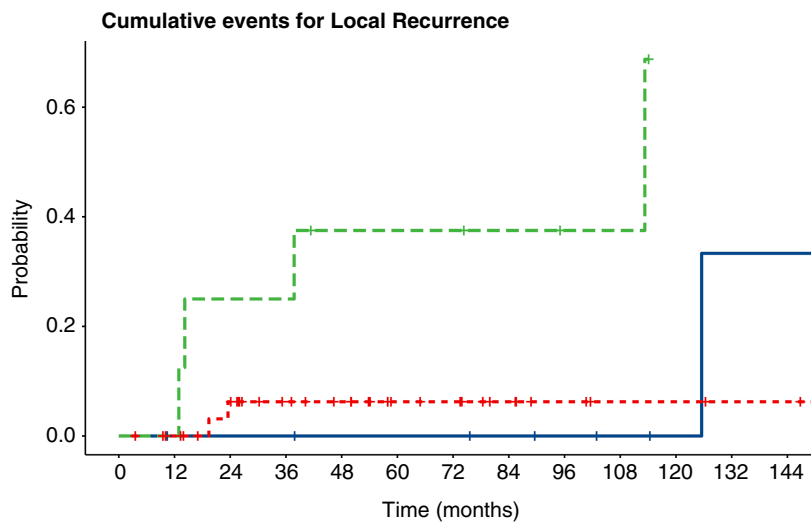


FIGURE 4 Local recurrence risk in patients with locally excised squamous cell carcinoma of the anal margin according to margin status.

	0	12	24	36	48	60	72	84	96	108	120	132	144
Involved margins	9	8	8	8	7	7	7	6	5	4	3	2	2
Clear margins	38	35	30	23	20	13	12	8	5	3	3	2	2
Fragmented / Unknown	8	8	6	6	4	4	4	3	2	2	0	0	0

DISCUSSION

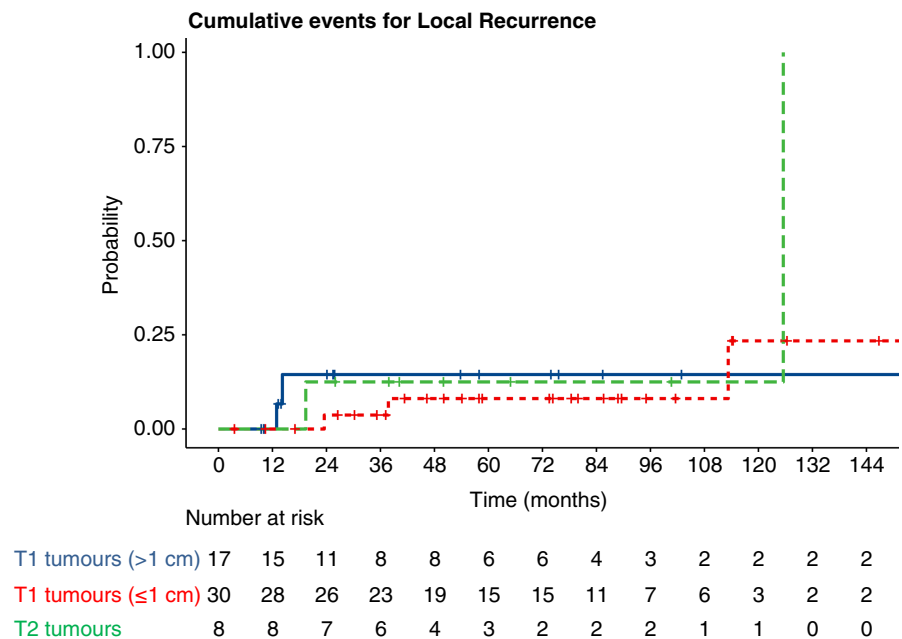
Anal cancers are uncommon tumours with 1500 cases diagnosed per year in the UK during 2016–2018 [15]. Of these, approximately 20% (<300 cases) arise from the anal margin and less than half may be amenable to LE alone. Although the mainstay of early-stage anal canal and margin cancer treatment is with CRT, early studies of this modality [16–18] did not include T1N0 disease, and subsequent landmark trials [19–23] only comprised 10%–15% of such patients [24]. As such, the applicability of CRT to all early-stage anal cancers

is uncertain and may lead to overtreatment of some patients if offered to all.

When assessing localized anal cancers, anal margin tumours should be distinguished as a separate disease entity from those arising from the anal canal. Wider margins can often be achieved on initial or further LE for anal margin tumours, but this is rarely achievable in anal canal tumours without encroaching into the internal (and sometimes the external) anal sphincter muscles, risking permanent faecal incontinence. Also, anal canal tumours probably have a higher risk of recurrence than anal margin tumours (based on a richer blood

Further oncological treatment	Outcome following recurrence
Single fraction of radiotherapy (10Gy)	Died after 27.9 months from starting treatment due to unrelated causes
5FU and MMC concurrently with radiotherapy (15 fractions, treatment not completed)	Died after 4.4 months from starting treatment due to unrelated causes
5FU and MMC concurrently with radiotherapy (completed 28 fractions of 50.4Gy)	Alive (currently at 130 months from starting treatment)
5FU and MMC concurrently with radiotherapy (completed 15 fractions of 30Gy)	Alive (currently at 107 months from starting treatment)
5FU and MMC concurrently with radiotherapy (completed 25 fractions of 45Gy)	Alive (currently at 85 months from starting treatment)
5FU and MMC concurrently with radiotherapy (completed 28 fractions of 50.4Gy)	Alive (currently at 56 months from starting treatment)
5FU and MMC concurrently with radiotherapy (completed 28 fractions of 50.4Gy)	Alive (currently at 33 months from starting treatment)
5FU and MMC concurrently with radiotherapy for local disease control (completed 28 fractions of 50.4Gy)	Died after 3.7 months from starting treatment
5FU and MMC concurrently with radiotherapy for local disease control (completed 27 fractions of 48.6Gy)	Died after 3.1 months from starting treatment

FIGURE 5 Local recurrence risk in patients with locally excised squamous cell carcinoma of the anal margin according to tumour size.



and lymphatic supply of the anal canal) which is not necessarily related to the excision margin or tumour size.

Our study demonstrates that LE alone of small (stage I and early stage II) anal margin tumours is associated with a low overall LR risk. Of the nine patients who had an initial involved RM (≤ 1 mm) but did not undergo further LE of the tumour bed/scar (either not fit or declined), there was no observed increase in LR risk at 3 or 5 years (Figure 4). Furthermore, we demonstrate that undertaking regular surveillance in patients with involved RM following initial or repeat LE and reserving CRT as salvage treatment on LR was effective in detecting LRs at an early stage during the follow-up period, with outcomes comparable to other modern studies [8, 25–29] (see Table 4).

This means that 88% of patients managed by LE alone who remained free of LR were spared the acute and late toxicities of CRT.

The risk of LR in locally excised anal margin tumours has not been previously correlated with the RM achieved, and in those with an involved RM appears lower than expected. Several reasons may explain this favourable result. First, most LE would have been performed using electrocautery. This creates a channel of thermal cellular ablation (fulguration), potentially destroying any viable cancer cells present at or near the margin of resection and creating an additional safety margin [30], albeit unintentional. Therefore, LE using electrocautery may result in a lower risk of LR than using sharp dissection with a scalpel in multiple settings. Second, the concept of a



TABLE 4 Summary of modern studies investigating anal margin cancer, including patient numbers, treatments and outcomes (all retrospective).

Study	Anal margin tumours treated by LE	Site	Involved margins	Adjuvant chemoradiotherapy	Locoregional recurrence	Distant metastases	5-year DFS	5-year OS	Comments
Badakhshi et al. [25]	10	Berlin, Germany (2000–2005)	Not clear	10/10 (100%)	Not clear	Not clear	54%	71%	T1–T2 anal margin and canal tumours grouped together. No definition of involved margins. Included node positive patients (14%)
Arana et al. [26]	17	Paris, France (2007–2009)	12 (70.6%)	12 (70.6%)	2 (11.7%)	Nil	87%	100%	Only 9/17 patients had anal margin tumours. Involved margins defined as ≤2 mm for anal canal and <1 cm for anal margin tumours
Alfa-Wali et al. [27]	15	London, UK (1986–2015)	Nil	Nil	Nil	Nil	100%	100%	Study looked at anal margin tumours in HIV patients. Involved margins defined as ≤5 mm
Leo et al. [28]	14	Perugia, Italy (2010–2015)	Not clear	Nil	Not clear	Not clear	Not clear	Not clear	Anal margin and canal tumours grouped together, as were CRT and surgery. Involved margins not defined. Unable to distinguish outcomes for LE
Renehan et al. [8]	35	Manchester, UK (2004–2017)	8 (22.9%)	10 (28.6%)	5 (14.3%)	1 (2.9%)	3-year DFS 84%	Not clear	Anal margin tumour series of T1 and T2 staging. Involved margins defined as ≤1 mm
McCabe et al. [29]	24	Bristol, UK (2007–2019)	13 (54.2%)	8 (33.3%)	3 (12.5%)	Not clear	78.4%	95.7%	Study included T1–T2 anal margin tumours. Involved margins defined as ≤1 mm
Roji et al. (2023), this study	55	Birmingham, UK (1999–2018)	9 (16.4%) Fragmented tumours 8 (14.5%)	Not included in study	7 (12.7%)	2 (3.6%)	82%	86%	Anal margin tumour series of T1 and T2 staging. Higher rates of local recurrence in fragmented tumours. Involved margins defined as ≤1 mm

Abbreviations: CRT, chemoradiotherapy; DFS, disease-free survival; HIV, human immunodeficiency virus; LE, local excision; OS, overall survival.

RM of <1mm rather than 0mm as being inadequate, which was established in the setting of total mesorectal excision for rectal cancer (mainly T3 disease) [31], is being challenged when applied to small lesions such as malignant colorectal polyps [32–34] and following transanal endoscopic microsurgery for early rectal cancer [35]. This study suggests that for small tumours, in the absence of other adverse features, the risk of LR in the presence of an RM of ≤ 1 mm probably remains quite low until the tumour is seen to reach the margin.

Patients with unknown initial RM/tumour fragmentation had a higher incidence of recurrence, regardless of undergoing further LE. It is likely that tumour fragmentation during attempted LE results in cell spillage and implantation. Fragmentation may also be a marker of poor surgical technique or simply reflect that these tumours were more 'locally advanced' and the fragmented tissue reflects a 'shave biopsy' rather than a complete LE. Therefore, fragmented tumours should be routinely regarded as inadequate (R1 or R2) resections.

Anal cancer patients with involved RM following LE are often routinely treated with adjuvant CRT. Currently, there is no consensus on the minimal RM considered to be adequate for LE specimens. Previously, >5mm was specified by ESMO-ESSO-ESTRO 2014 [4] whilst >10mm was specified by the NCCN 2018 [11] and ASCRS 2018 [12] guidelines. In practice, such margins are rarely achievable or realistic. Indeed, in our cohort, only 5.5% and 1.8% of patients had RMs of >5 and >10mm respectively. Usage of such margins to determine adequate/inadequate resections will lead to the vast majority of patients, perhaps unnecessarily, being recommended for adjuvant CRT [8]. Furthermore, the pursuance of such margins during resection will lead to increased surgical morbidity [8]. Our centre has used a >1mm margin as an arbitrary cut-off since 2004 but we have carefully monitored cumulative LR rates prospectively for over 10 years. The ongoing UK NCRI PLATO (ACT3) trial has also adopted a >1mm margin cut-off in small anal margin tumours [7], as have the most recent ESMO 2021 guidelines [36].

The management of anal cancers at QEHB has evolved since the formation of the regional anal cancer MDT in 2004. Most patients (65%) with anal cancer are initially investigated at their local hospital and are only referred to QEHB for further treatment once a histological diagnosis has been established. In many cases, the anal margin lesions were not suspected to be malignant in nature, and LE was performed mainly as a diagnostic excision biopsy with minimal peripheral and deep margins rather than as an oncological therapeutic procedure. In this situation, the anal cancer MDT will review the histology of the excised specimen to confirm the presence of invasive SCC, to assess the completeness (margins) of LE and to examine the patient for residual macroscopic disease (R2 resection), to decide on subsequent management. This explains the high rate (47.3%) of initial R1 resection referrals received. For the few patients with clinically suspected but unconfirmed SCC, the anal cancer MDT surgeons were able to perform a primary therapeutic wide excision. All referrals are prospectively recorded onto a database and mature follow-up data are available for most patients. The catchment

population of patients covered by QEHB and its surrounding referring hospitals is large (approximately 2.2 million) and stable, with few patients being lost to follow-up. Therefore, although the total number of patients presented in this study may appear small, to date we believe this to be the largest published series of anal margin cancer patients treated by LE alone, correlating RM and tumour size with data on local/distant recurrence.

During the study period, we tried to avoid giving adjuvant CRT to anal margin cancer patients with involved RM for several reasons. First, radiotherapy at the time (up to 2014) was delivered to large pelvic volumes via 2D and/or 3D conformal techniques and was associated with significant acute and long-term toxicities [20, 21, 37] including risk of anal sphincter and pelvic nerve dysfunction, infertility and impaired sexual function, radiation-induced menopause, chronic small bowel and pelvic bone complications.

Many patients reported a significant reduction in quality of life following CRT [38], and approximately 1% died of CRT-related complications [23]. There was also an increased risk of death (9.1%) from non-anal cancer causes in the first 5 years following CRT, mainly from cardiovascular toxicity related to chemotherapy use and from second malignancies [39]. The routine use of intensity modulated radiotherapy techniques has reduced the toxicities of pelvic CRT [40–42], but it still entails potential complications which are not insignificant and sometimes difficult to justify for small anal margin tumours. Until commencement of the PLATO ACT3 trial, there was no consensus on the use of involved field low dose adjuvant CRT in anal margin cancers. Second, the risk and pattern of recurrence in this group has not been sufficiently described to relate the benefits of adjuvant CRT to the underlying risk, and to guide optimal radiotherapy volumes. Third, it was felt likely that LR at the anal margin would be detected early through regular surveillance where patients were encouraged to immediately report any change in this intimate area. Therefore, when offered the choice between adjuvant CRT or regular surveillance, the majority of those with involved RM chose the latter, with only two patients opting for adjuvant CRT (excluded from analysis) (Figure 1). By undergoing regular surveillance, these patients were spared the adverse effects of pelvic CRT while preserving the scope for future radiotherapy to the pelvis, either for recurrence or for other unrelated malignancies should this be required.

We acknowledge several limitations to this study. First, although it is one of the largest series of anal margin tumours reported, the sample size remains underpowered to reach definite conclusions on the correlation between RM and LR due to the small number of events. Second, not all patients had pre-/post-LE staging imaging. However, most of those who did not have imaging had very small T1 tumours (<1cm) as they were deemed to be at extremely low risk of pelvic lymph node or distant metastatic disease at presentation. We did not observe any such events in this group within 2 years of LE. Third, although routine HIV testing was not performed in most patients during this period it was targeted at patients thought to be at potential risk (i.e., intravenous drug users, men who have sex with men [MSM]). No new HIV cases

have been seen in this cohort during the follow-up period. Lastly, most patients were referred from multiple centres by multiple surgeons following LE, with limited surgical data available. The LE specimens were reported by multiple pathologists with inconsistent documentation of the actual size of the invasive tumour component and RMs. Although some of these data were obtainable on histology review by the anal cancer MDT pathologist at the QEHB, other recognized potential risk factors such as perineural/lymphatic/vascular invasion could not be evaluated. Due to this, we were only able to evaluate the effects of tumour size and RMs on LR, as these were the only data consistently available. However, whilst this might be considered by some to be a limitation, we believe that this study reflects the 'real world' experience. Most LE lesions were unsuspected by the operating surgeon, and it would be impracticable and inappropriate for all questionable anal lesions to be referred to the anal cancer MDT. It does emphasize, however, the importance of accurate operative documentation by referring surgeons, which can inform subsequent decision making.

CONCLUSION

Our findings are that most small and localized anal margin tumours can be adequately treated by LE alone with low LR rates (unless fragmented) and can be successfully salvaged with CRT when necessary. This potentially spares many anal margin tumour patients the toxicities of CRT and preserves the scope for pelvic radiotherapy in the future. The UK NRCI PLATO ACT3 trial is investigating a similar group of patients with locally excised T1N0 anal margin tumours, with an observational arm for those with margins >1 mm and an adjuvant reduced-dose involved field CRT arm for those with margins ≤1 mm. We believe our study will complement the PLATO ACT3 results, by highlighting the feasibility and safety of treating small anal margin tumours with LE alone, providing the excision margin is adequate, and deferring adjuvant CRT as salvage treatment on LR through regular follow-up.

FUNDING INFORMATION

This project formed part of Dr KF Namiq's University of Birmingham MSc in Clinical Oncology thesis, which was sponsored by the Higher Committee for Education Development in Iraq—HCED. No other sources of funding were received during the study.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT AND PATIENT CONSENT

The study was approved by our local audit management board which gave permission to proceed without further patient consent due to

the retrospective nature of the data analysis. Patient details were anonymized during data analysis and when presented within the paper.

ORCID

A. M. Roji <https://orcid.org/0000-0002-7671-2341>

REFERENCES

- Johnson LG, Madeleine MM, Newcomer LM, Schwartz SM, Daling JR. Anal cancer incidence and survival: the surveillance, epidemiology, and end results experience, 1973–2000. *Cancer*. 2004;101(2):281–8.
- Wilkinson JR, Morris EJ, Downing A, Finan PJ, Aravani A, Thomas JD, et al. The rising incidence of anal cancer in England 1990–2010: a population-based study. *Colorectal Dis*. 2014;16(7):O234–9.
- Clark MA, Hartley A, Geh JI. Cancer of the anal canal. *Lancet Oncol*. 2004;5(3):149–57.
- Glynn-Jones R, Nilsson PJ, Aschele C, Goh V, Peiffert D, Cervantes A. Anal cancer: ESMO-ESSO-ESTRO clinical practice guidelines for diagnosis, treatment, and follow-up. *Radiother Oncol*. 2014;111(3):330–9.
- Jemal A, Simard EP, Dorell C, Noone AM, Markowitz LE, Kohler B. Annual report to the nation on the status of cancer, 1975–2009, featuring the burden and trends in human papillomavirus (HPV)-associated cancers and HPV vaccination coverage levels. *J Natl Cancer Inst*. 2013;105:175–201.
- Hatfield P, Cooper R, Sebag-Montefiore D. Involved-field, low-dose chemoradiotherapy for early-stage anal carcinoma. *Int J Radiat Oncol Biol Phys*. 2008;70(2):419–24.
- Sebag-Montefiore D, Adams R, Bell S, Berkman L, Gilbert DC, Glynn-Jones R, et al. The development of an umbrella trial (PLATO) to address radiation therapy dose questions in the locoregional management of squamous cell carcinoma of the anus. *Int J Radiat Oncol Biol Phys*. 2016;96(2):E164–5.
- Rehnan AG, Muirhead R, Berkman L, Sebag-Montefiore D. Early stage anal margin cancer: towards evidence-based management. *Colorectal Dis*. 2019;21:387–91.
- Werner RN, Gaskins M, Valle GA, Budach V, Koswig S, Mosthaf FA, et al. State of the art treatment for stage I to stage III anal squamous cell carcinoma: a systemic review and meta-analysis. *Radiother Oncol*. 2021;157:188–96.
- Geh I, Gollins S, Rehnan A, Scholefield J, Goh V, Prezzi D, et al. Association of Coloproctology of Great Britain and Ireland (ACPGBI): guidelines for the management of cancer of the colon, rectum and anus (2017)—anal cancer. *Colorectal Dis*. 2017;19:82–97.
- NCCN clinical practice guidelines in oncology, version 2.2018 [Internet]. [cited 2019 May 12]. Available from: http://www.nccn.org/professionals/physician_gls/pdf/anal.pdf
- Stewart DB, Gaertner WB, Glasgow SC, Herzig DO, Feingold D, Steele SR. The American Society of Colon and Rectal Surgeons clinical practice guidelines for anal squamous cell cancers (revised 2018). *Dis Colon Rectum*. 2018;61:755–74.
- Quirke P, Dixon M, Durdey P, Williams N. Local recurrence of rectal adenocarcinoma due to inadequate surgical resection: histopathological study of lateral tumour spread and surgical excision. *Lancet*. 1986;328(8514):996–9.
- Birbeck KF, Macklin CP, Tiffin NJ, Parsons W, Dixon MF, Mapstone NP. Rates of circumferential resection margin involvement vary between surgeons and predict outcomes in rectal cancer surgery. *Ann Surg*. 2002;235(4):449–57.
- Cancer Research UK [Internet]. [cited 2019 May 12]. Available from: <https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/anal-cancer/incidence>

16. Nigro ND, Vaitkevicius VK, Considine BR. Combined therapy for cancer of the anal canal: a preliminary report. *Dis Colon Rectum*. 1974;17(3):354–6.
17. Cummings BJ, Harwood AJ, Keane TJ, Thomas GM, Rider WD. Combined treatment of squamous cell carcinoma of the anal canal: radiation therapy with 5-fluorouracil and mitomycin-C, a preliminary report. *Dis Colon Rectum*. 1980;23(6):389–91.
18. Nigro ND, Seydel HG, Considine B, Vaitkevicius VK, Leichman L, Kinzie JJ. Combined preoperative radiation and chemotherapy for squamous cell carcinoma of the anal canal. *Cancer*. 1983;51(10):1826–9.
19. UKCCCR Anal Cancer Trial Working Party. Epidermoid anal cancer: results from the UKCCCR randomised trial of radiotherapy alone versus radiotherapy, 5-fluorouracil, and mitomycin. *Lancet*. 1996;348(9034):1049–54.
20. Bartelink H, Roelofsen F, Eschwege F, Rougier P, Bosset JF, Gonzalez DG, et al. Concomitant radiotherapy and chemotherapy is superior to radiotherapy alone in the treatment of locally advanced anal cancer: results of a phase III randomized trial of the EORTC Radiotherapy and Gastrointestinal Cooperative Groups. *J Clin Oncol*. 1997;15(5):2040–9.
21. Flam M, John M, Pajak TF, Petrelli N, Myerson R, Doggett S, et al. Role of mitomycin in combination with fluorouracil and radiotherapy, and salvage chemoradiation in the definitive nonsurgical treatment of epidermoid carcinoma of the anal canal: results of a phase III randomized intergroup study. *J Clin Oncol*. 1996;14(9):2527–39.
22. Gunderson LL, Winter KA, Ajani JA, Pedersen JE, Moughan J, Benson AB 3rd, et al. Long-term update of US intergroup RTOG 98-11 phase III trial for anal carcinoma: survival, relapse, and colostomy failure with concurrent chemoradiation involving fluorouracil/mitomycin versus fluorouracil/cisplatin. *J Clin Oncol*. 2012;30(35):4344–51.
23. James RD, Glynn-Jones R, Meadows HM, Cunningham D, Myint AS, Saunders MP, et al. Mitomycin or cisplatin chemoradiation with or without maintenance chemotherapy for the treatment of squamous-cell carcinoma of the anus (ACT II): a randomised, phase 3, open-label, 2 × 2 factorial trial. *Lancet Oncol*. 2013;14(6):516–24.
24. Chai CY, Tran Cao HS, Awad S, Massarweh NN. Management of stage I squamous cell carcinoma of the anal canal. *JAMA Surg*. 2018;153(3):209–15.
25. Badakhshi H, Budach V, Wust P, Graf R. Anal carcinoma: surgery does not influence prognosis when performed prior to concurrent radiochemotherapy. *Anticancer Res*. 2013;33:4111–6.
26. Arana R, Flejou JF, Si-Mohamed A, Bauer P, Etienney I. Clinicopathological and virological characteristics of superficially invasive squamous-cell carcinoma of the anus. *Colorectal Dis*. 2015;17:965–72.
27. Alfa-Wali M, Dalla Pria A, Nelson M, Tekkis P, Bower M. Surgical excision alone for stage T1 anal verge cancers in people living with HIV. *Eur J Surg Oncol*. 2016;42(6):813–6.
28. Leo CA, Santorelli C, Hodgkinson JD, Bidovaneta O, Baldelli F, Cantarella F, et al. Five year experience of the treatment of squamous cell carcinoma of the anus. *G Chir*. 2017;38(4):176–80.
29. McCabe T, Parwaiz I, Longman RJ, Thomas MG, Messenger DE. Outcomes following local excision of early anal squamous cell carcinomas of the anal canal and perianal margin. *Colorectal Dis*. 2020;23:689–97.
30. Memon MA. Surgical diathermy. *Br J Hosp Med*. 1994;52(8):403–8.
31. Wibe A, Rendedal R, Svensson E, Norstein J, Eide TJ, Myrvold HE, et al. Prognostic significance of the circumferential resection margin following total mesorectal excision for rectal cancer. *Br J Surg*. 2002;89:327–34.
32. Naqvi S, Burroughs S, Chave HS, Branagan G. Management of colorectal polyp cancers. *Ann R Coll Surg Engl*. 2012;94:574–8.
33. Berg KB, Telford JJ, Gentile L, Schaeffer DF. Re-examining the 1-mm margin and submucosal depth of invasion: a review of 216 malignant colorectal polyps. *Virchows Arch*. 2020;476:863–70.
34. Gill MD, Rutter MD, Holtham SJ. Management and short-term outcome of malignant colorectal polyps in the north of England. *Colorectal Dis*. 2013;15(2):169–76.
35. Bach SP, Hill J, Monson JR, Simson JN, Lane L, Merrie A. A predictive model for local recurrence after transanal endoscopic microsurgery for rectal cancer. *Br J Surg*. 2009;96(3):280–90.
36. Rao S, Guren MG, Khan K, Brown G, Renehan AG, Steigen SE, et al. Anal cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2021;32(9):1087–100.
37. Anjani JA, Winter KA, Gunderson LL. Fluorouracil, mitomycin, and radiotherapy vs fluorouracil, cisplatin, and radiotherapy for carcinoma of the anal canal: a randomized controlled trial. *JAMA*. 2008;299(16):1914–21.
38. Bentzen AG, Balteskard L, Wanderas EH, Frykholm G, Wilsgaard T, Dahl O, et al. Impaired health-related quality of life after chemoradiotherapy for anal cancer: late effects in a national cohort of 128 survivors. *Acta Oncol*. 2013;52(4):736–44.
39. Northover J, Glynn-Jones R, Sebag-Montefiore D, James R, Meadows H, Wan S, et al. Chemoradiation for the treatment of epidermoid anal cancer: 13-year follow-up of the first randomised UKCCCR Anal Cancer trial (ACT I). *Br J Cancer*. 2010;102:1123–8.
40. Kachnic LA, Winter K, Myerson RJ, Goodyear MD, Willins J, Esthappan J, et al. RTOG 0529: a phase 2 evaluation of dose-painted intensity modulated radiation therapy in combination with 5-fluorouracil and mitomycin-c for the reduction of acute morbidity in carcinoma of the anal canal. *Int J Radiat Oncol Biol Phys*. 2013;86(1):27–33.
41. Tozzi A, Cozzi L, Iftode C, Ascolese A, Campisi MC, Clerici E, et al. Radiation therapy of anal canal cancer: from conformal therapy to volumetric modulated arc therapy. *BMC Cancer*. 2014;14:833.
42. Muirhead R, Drinkwater K, O’Cathail SM, Adams R, Glynn-Jones R, Harrison M, et al. Initial results from the Royal College of Radiologists’ UK National Audit of anal cancer radiotherapy 2015. *Clin Oncol (R Coll Radiol)*. 2017;29(3):188–97.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Roji AM, Namiq KF, Radley S, Ismail T, Hejmadi R, Taniere P, et al. Management of small (T1–T2) anal margin squamous cell carcinoma: clinical outcomes following local excision alone. *Colorectal Dis*. 2023;25:1403–1413. <https://doi.org/10.1111/codi.16562>