Article:
Renehan, AG, Muirhead, R, Berkman, L et al. (3 more authors) (2019) Early stage anal margin cancer: towards evidence-based management. Colorectal Disease. ISSN 1462-8910

https://doi.org/10.1111/codi.14571

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Article type : For Debate

Early stage anal margin cancer: towards evidence-based management

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Keywords: anal cancer; local excision; chemo-radiotherapy

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What is the significance of this paper?

This debate paper summarises the rationale and design of the ACT3 component of the UK national PLATO anal cancer umbrella trial. The results from this trial will, for the first time, provide an evidence base for the management of early stage anal margin cancers.

Anal squamous cell carcinoma is an uncommon Human Papilloma Virus (HPV)-related malignancy, the incidence of which has increased two- to four-fold over the past three decades [1, 2]. Results from the first three phase III trials, performed in the 1990s (the largest being the ACT I trial in the UK [3]), established concurrent mitomycin C (MMC), 5-fluorouracil chemotherapy and radiotherapy (CRT) as the main primary treatment. Three subsequent trials (including ACT II in the UK [4]), performed between 1998 and 2008, demonstrated evidence of no benefit from the use of additional chemotherapy before or after

CRT, or concurrent cisplatin. These trials broadly used a “one size fits all” radiotherapy approach for a wide spectrum of the loco-regional disease stages at presentation.

Today, patients undergo staging pelvic MRI, and increasingly FDG-PET, to better define tumour (T) and nodal (N) stage. While these new imaging technologies have some weaknesses in clinic (for example, imperfect specificity for nodal involvement [5]), there are nonetheless greater opportunities to identify sub-groups that require stratified approaches to treatment. One such subgroup is early stage cancer (T1N0) of the anal margin, which to-date has been understudied. The anal margin is defined as the pigmented skin immediately surrounding the anal orifice, extending laterally to a radius of approximately 5 cm. Clinical trial data indicate that 12% [4] to 23% [3] of anal cancers arise from the margin, but these statistics only account for patients undergoing CRT. We estimate that only 4% of all anal cancers are anal margin tumours treated by local excision (LE) [6]. The oncological principles in this setting are: complete excision of T1N0 tumours is achievable in many patients without major surgical morbidity, with avoidance of the CRT-related morbidity, and a low risk of subsequent local relapse or nodal spread.

However, large-scale data to support the above principles are lacking. In the literature, studies are mainly historical small retrospective case series (**Table 1**) [7-13]. There is heterogeneity of tumour stages and treatments and a lack of definition and reporting of histological margin involvement. Some centres used post-excision radiotherapy, generally without clear selection criteria, such that the results of this strategy are unclear.

Until the 7th Edition of the AJCC Staging System (2009) [14], anal margin cancers were staged by skin cancer criteria. In the latest 8th Ed AJCC [15], the criteria were revised in line with anal canal cancers. Nonetheless, there remains a historical misconception that these tumours are similar to skin cancers. The latter are routinely treated with repeated excision but the perianal anatomy limits the usefulness of this strategy, and experience shows that repeated excision results in significant morbidity. By contrast, HPV-related anal

cancers are radiosensitive and lower doses are likely to achieve excellent outcomes for residual microscopic disease, with less toxicity in comparison with higher doses required to treat skin cancers.

For early stage anal margin tumours, the 2014 ESMO guidelines [16] recommended > 5 mm surgical clearance, presumably based on principles for skin cancers. These guidelines state that a poorly differentiation histology is a contra-indication to LE, but as Table 1 indicates, there is a paucity of data to support this. The 2017 ACPGBI guidelines [17] state that "the tumour should be excised with a margin of normal perianal skin and deeper tissue" – but without defining a clear margin. Thus, there is a dilemma. The results of some series, such as those from Manchester **(Table 1)**, suggest that selective CRT is appropriate, whereas if the ESMO guidelines were followed, nearly all patients should require post-excision CRT.

The PLATO (PersonaLisingrAdioTherapydOse in anal cancer, ISRCTN88455282) trial [18] is a single protocol 'platform' comprising the ACT3, 4 and 5 trials with the aim of personalising radiotherapy dose across the spectrum from early to locally advanced stage disease. The ACT3 trial is designed as a non-randomised, phase II multi-centre trial in patients with T1N0 anal margin cancers. It assesses a pre-defined treatment strategy using LE for T1N0 anal margin tumours. Patients with margins >1 mm undergo active surveillance; whereas selective post-excision low-dose involved field CRT (41.4Gy in 23 fractions with concurrent day 1 MMC and capecitabine 825mg/mg bd on days of radiotherapy) will be used for patients with close or positive margins **(Figure 1)**. Due to the lack of high quality evidence, a consensus view† was developed where we defined an involved margin as microscopic carcinoma present ≤ 1mm at the lateral or deep margin. To address the concern that conventional post-excision CRT is associated with considerable morbidity, there is a rationale for the use of lower dose radiotherapy underpinned by previous published studies [19, 20] and modelling [21] of treatment doses lower than those conventionally used.

ACT3 will recruit ninety eligible patients, who have undergone LE, and aims to demonstrate a 3-year loco-regional failure rate of <10% following frequent clinical assessments (3 monthly in first 2 years; 6 monthly in year 3) and pelvic MR imaging at 12 and 36 months. In PLATO ACT3, the strategy of low dose CRT for margins ≤1 mm will discourage ad hoc use of post-excision CRT and the practice of repeated excisions.

Recruitment commenced in January 2017. Patients who consent to participate in ACT3 will know their proposed treatment approach as this is defined by margin status (the study is not randomised). The first year identified barriers to recruitment, which we are addressing. First, while patients may present through several clinical routes, we expect most will come through colorectal surgeons. There are clear opportunities for this surgical community to be pivotal in identifying potential patients and referring these timely to the regional anal cancer MDT for trial recruitment. Second, we have recently widened the inclusion criteria to include piecemeal excisions to reflect presentations in clinical practice – for example, after haemorrhoidectomy - provided there is source data documentation prior to excision that the lesion was <2 cm. Third, there is a subset of patients with asymptomatic anal cancer excised on surveillance which have recently been defined by the LAST consensus as 'superficially invasive squamous-cell carcinoma' (SISCCA) of the anus. SISCCA is defined as an invasive squamous cell carcinoma that (i) has an invasive depth of ≤3 mm from the basement membrane, and (ii) has a horizontal spread of ≤7 mm in maximal extent, and (iii) has been completely excised [22]. These lesions are superficial when present in the anal margin skin and are limited to the mucosa in the anal canal, contrasting with larger lesions of the anal canal for which local excision is contra-indicated [16, 23].

In this understudied group of early stage anal cancers, where management is currently heterogeneous, we hope to define strategy suitable for international use through the ACT3 trial.

Table 1 Local excision for anal margin cancer - summary of numbers, treatments and outcomes from literature review

Authors	Institute	Totals	SCC under going LE	Mean age (years)	Positive margin	Ano-rectal site relapse	Oncological outcomes: Nodal met.	Distant met.	Any death	5 year survival	Comments
Beahrs et al. 1976 [8]	Mayo Clinic 1950-70 Cleveland	31	27	Not clear	Not clear	7/19 (37%)	-	-	-	82%	27 of the 31 treated by LE; remaining four by radiation only. It becomes clearer later in the paper that at least 9 LEs received radiation.
Al-Jurf et al. 1979 [7]	Clinic 1951-71 University of	17	10	Not clear	Not clear	3/10 (30%)	-	-	-	-	7 of the 17 initial patients were recurrent cases treated by salvage APR
Schraut et al. 1983 [12]	Chicago 1953-80	52	16	24 to 88	Not clear	4/18 (22%)	-	-	2	80%	
Greenall et al. 1985 [9]	MSKCC 1950-81	48	31	56	Not clear	4/24* (17%)	-	-	-	-	Included cases treated by LE and APR. Classified as 'superficial' and 'deep' invasion. We suspect the latter applies to APR rather than LE excised specimens
Merlini & Eckert 1985 [10]	Lausanne, Switzerland 1942-83	16	14	64	Not clear	not presented	-	-	3	-	Included cases treated by LE and APR. 3 deaths attributed to the disease
Pintor et al. 1989 [11]	St Marks, London 1948-84	228	49	60.7	Not clear	not presented	-	-	-	69%	Pathologies included non-invasive lesions. 8 had additional radiotherapy
Leon et al. 2018 [13]	Nordic anal cancer database 2000-2007	93 TxT1–2N0M0 SCC treated with surgery alone (n: 59) or surgery plus RT/CRT (n: 34).		Medians: 55.5 to 66	Not clear	7/23 (30%)	-	-	-	-	Included anal canal and margin cancers treated by surgery, including LE and APR. Some patients has post-excision RT. It was not possible to disentangle the outcomes from these different treatment pathways
Christie, Manchester 2004-17‡		823	35 (4%)	52.6	†T1N0: 5/21 (24%) T2N0: 3/12 (25%)	†T1N0: 2/21 (10%) T2N0: 2/12 (17%)	†T1N0: 0/21 (0%) T2N0: 1/12 (8%)	†T1N0: 0/21 (0%) T2N0: 1/12 (8%)	†4 of 33 (12%)	T1-2N0: 3-year DFS: 84%	T1N0: 7/21 (33%) received RT or CRT; T2N0: 3/12 (25%) received RT or CRT. 4 deaths: 3 non-cancer; one cancer-related

SCC: squamous cell carcinoma. met.: metastasis. LE: local excision. APR: abdomino-perineal resection. DFS: disease-free survival. RT: radiotherapy. CRT: chemo-radiotherapy. MSKCC: Memorial Sloan-Kettering Cancer Centre.
*Only 24 had sufficient follow-up.
† Reported by T1N0 and T2N0 to mimic the question being asked in PLATO ACT3. Two patients with node positive at presentation excluded from analysis.
‡ See acknowledgements for contributors

Conflict of interest:

AGR has received speaker honoraria from Merck Serona and Jenssen-Cilag on unrelated topics, in the last two years. The other authors have nothing to declare.

Acknowledgments:

†The PLATO trial management group (TMG) includes: Rebecca Muirhead (Oxford, UK), Andrew Renehan (Manchester, UK) - ACT3 leads; Richard Adams (Cardiff, UK), Mark Harrison (Mount Vernon, London, UK) – ACT4 leads; David Sebag-Montefiore (Leeds, UK), Maria Hawkins (Oxford, UK) - ACT 5 leads. Other TMG members include: Rob Glynne-Jones (Mount Vernon, London, UK), Duncan Gilbert (Brighton, UK), Vicky Goh (London,

UK), Phil Quirke (Leeds, UK), Gordon Hutchins (Leeds, UK), Galina Velikova (Leeds, UK), Lindy Berkman (PPI), Sheela Rao (Royal Marsden, London UK), Jenny Seligman (Leeds, UK), Natalie Abbott (RTQA); Alex Smith, Lucy McParland, Jo Webster, Sue Bell, Amanda Langley, Simone Ryan, Walter Gregory, Leeds CTRU, UK)

‡ The Christie Manchester series recognises that many surgeons from around Greater Manchester and the North West of England referred patients for follow-up after first surgery at their local hospital. The data reported for the Christie Anal Cancer MDT acknowledges the long-term (since 2004) input to management of these patients from Sarah T O'Dwyer, Malcolm S Wilson, Paul E Fulford, and Mark P Saunders, and the input on earlier data collection by Tim Bullen.

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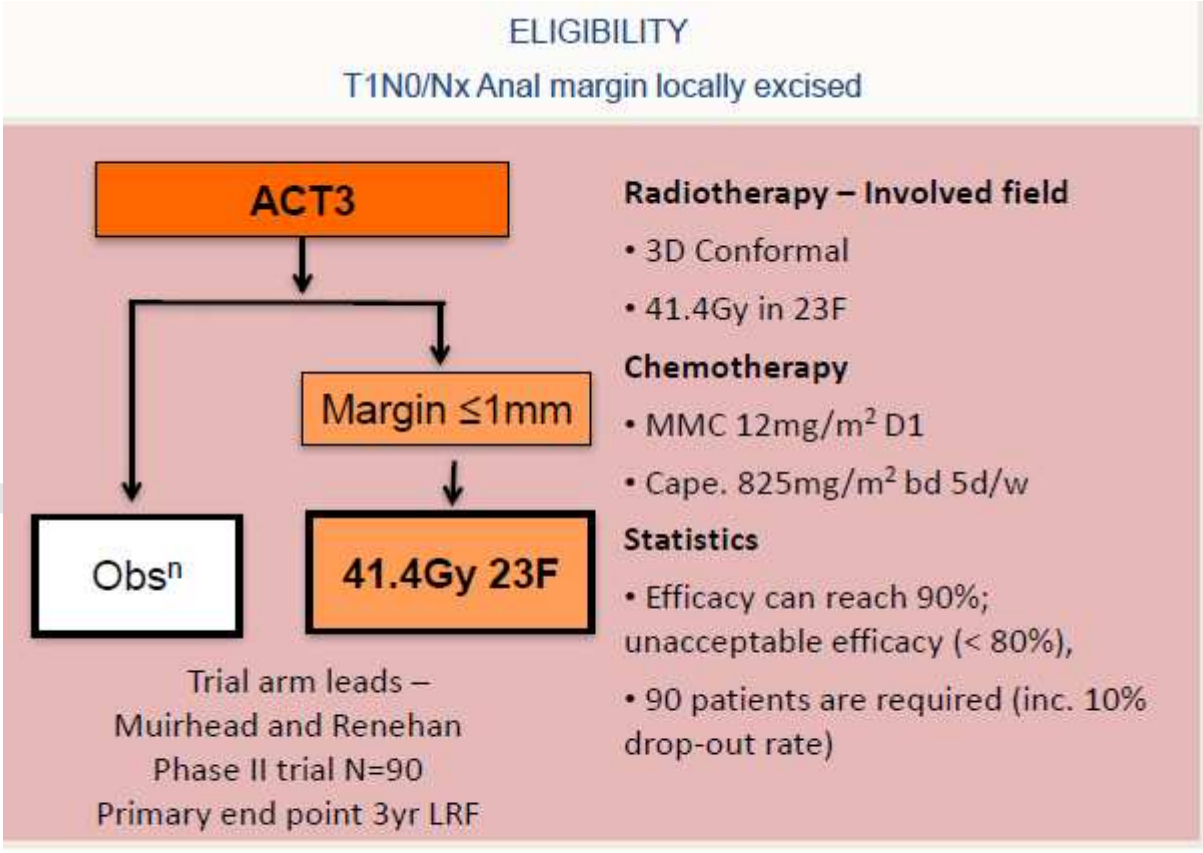

Figure 1 Trial schema for ACT3. Obsⁿ: observation arm.. MMC: mitomycin. Cape: capecitabine. LRF: loco-regional failure.