Proceedings Paper:
Theophanous, S., Samuel, R., Lilley, J. et al. (4 more authors) (2022) PO-1321 Prognostic factors for anal cancer treated with conformal radiotherapy – a systematic review. In: Radiotherapy and Oncology. ESTRO 2022, 06-10 May 2022, Copenhagen, Denmark/Online. Elsevier , S1115-S1116.

https://doi.org/10.1016/s0167-8140(22)03285-6

SCAN ME to find out more

Prognostic factors for anal cancer treated with conformal radiotherapy – a systematic review

Stelios Theophanous[1], Robert Samuel[1], John Lilley[2], Ann Henry[1], David Sebag-Montefiore[1], Alexandra Gilbert[1], Ane L Appelt[1,2]

[1]Leeds Institute of Medical Research at St James's, University of Leeds, Leeds, UK; [2]Department of Medical Physics, Leeds Cancer Centre, St James's University Hospitals, Leeds, UK

INTRODUCTION

- Anal cancer is a rare disease with an increasing incidence rate. Concurrent chemoradiotherapy is the standard of care for localised anal cancer.
- The introduction of three-dimensional conformal radiotherapy (3D-CRT), intensity modulated radiotherapy (IMRT) and latterly volumetric arc therapy (VMAT) has allowed for substantial reduction in dose to pelvic organs at risk and associated toxicity, resulting in far fewer unplanned treatment breaks.
- Due to the cancer's rarity, only a handful of late phase clinical trials have been conducted over the last four decades. These trials were conducted prior to widespread adoption of conformal radiotherapy techniques.
- Much of the published literature on prognostic factors in anal cancer consists of retrospective series, often small cohorts or cohorts of patients treated with outdated techniques.
- No systematic review of studies identifying prognostic factors for anal cancer outcomes after treatment with conformal radiotherapy has previously been conducted.

AIM

This systematic review aims to identify prognostic factors for a variety of outcomes in anal cancer, focusing on patients treated with curative intent using conformal radiotherapy techniques and contemporary treatment schedules.

METHODS

- This systematic review was undertaken according to the PRISMA 2020 guidelines.
- A literature search was conducted using the Medline and Embase databases (Table 1). Two reviewers screened and assessed all relevant articles.
- The methodological quality of all selected articles was assessed independently by two reviewers using the National Institutes of Health Quality Assessment Tool for Case Series Studies.
- Relevant data was extracted from the selected articles for further analysis.
- Reported outcomes and outcome definitions were stratified into nine categories. Disease activity and survival outcomes were firstly grouped according to the CORMAC review. Additional categories were inductively derived after the data extraction process.
- For each study, factors analysed for their prognostic impact were extracted, whether they were shown to have a significant relationship with outcome, and the statistical method used for analysis. The factors were grouped into three broader categories: **clinical factors, biomarkers and imaging factors.**
- Prognostic factors which were identified as significant in each study, along with their respective factor effect in the form of hazard ratios were extracted. Only factors reported as prognostic in more than one study were included in the final results.

Search string
'**radiotherapy**' AND '**anal cancer**' AND '**prognostic factor**', as well as related terms

Inclusion criteria	Exclusion criteria
• At least 70% of patients treated with conformal radiotherapy techniques	• Patients treated with 2D radiotherapy techniques and/or fields based solely on bony landmarks
• Published between 1st Jan 2000 and 30th June 2020	• Patients treated with palliative intent
• Reported survival or disease-related outcomes	• Cohort consisted of less than 100 patients
• Examined prognostic factors for outcomes using univariable or multivariable analysis	• Cohort derived from population level databases
	• Meta-analysis studies, reviews, animal model studies, conference abstracts and studies without English translation

Table 1. Summary of the search strategy used to identify relevant articles. The criteria used during the study screening and eligibility process are included.

RESULTS

Outcome (number of studies reporting outcome)	Factor	Times identified as prognostic	Studies which identified factor as prognostic
Overall survival (n=17)	Male sex	7	[1], [2], [6], [8], [9], [10], [14]
	Higher T stage	3	[3], [12], [14]
	Older age	3	[5], [14], [14]
	Higher N stage	3	[6], [7], [13]
	Higher AJCC stage	2	[3], [15]
	Leukocytosis	2	[10], [13]
	Neutrophilia	2	[10], [13]
Locoregional control (n=11)	Male sex	4	[1], [2], [8], [10]
	Higher N stage	3	[1], [2], [11]
	Incomplete/interrupted RT	2	[1], [3]
	Worse performance status	2	[5], [10]
	Lower HPV16 load	2	[8], [9]
Disease-free survival (n=11)	Male sex	4	[2], [8], [10], [14]
	Higher T stage	3	[3], [4], [14]
	Higher N stage	2	[2], [4]
	Leukocytosis	2	[10], [13]
	Neutrophilia	2	[10], [13]
	Anaemia	2	[10], [13]
Metastasis-free survival (n=5)	Male sex	2	[2], [4]
	Higher T stage	2	[2], [3]
	Higher N stage	2	[2], [11]
Freedom from disease (n=4)	Male sex	2	[1], [9]
Colostomy-free survival (n=4)	Higher T stage	3	[3], [7], [14]

Table 2. Clinical factors and biomarkers identified as prognostic for worse outcomes by more than one study through multivariate analysis, stratified by outcome.

- 19 studies were included and analysed in this literature review; all were retrospective case series, and were either single institutional (n=10) or multi-institutional (n=9).
- In terms of methodological quality, 16 were deemed good and three were deemed fair.
- Patients were treated between 1989-2018 with a median follow-up range of 14.9-70.0 months. The most common radiotherapy techniques employed were a combination of 3D-CRT and IMRT/VMAT (n=9), followed by IMRT only (n=6). Dose ranged from 45Gy/25 fractions to 63Gy/35 fractions and chemotherapy regimens were mainly Mitomycin C and 5-Fluorouracil based.
- The most commonly investigated outcomes were overall survival, locoregional failure and disease-free survival. Outcome definitions varied considerably between studies.
- In both univariable and multivariable analysis, N stage, T stage, and sex were found to be the most prevalent and reliable clinical prognostic factors for the majority of outcomes explored (Table 2).
- Only a few biomarkers have been identified as prognostic by more than one study – pre-treatment biopsy HPV load, as well as the presence of leukocytosis, neutrophilia and anaemia at baseline measurement.
- There is a lack of studies exploring the prognostic significance of imaging factors.

CONCLUSIONS

Identified prognostic factors: T stage, N stage, sex, pre-treatment biopsy HPV load, presence of baseline leukocytosis, neutrophilia and anaemia.

The identification of these prognostic factors may help improve the design and analysis of new clinical trials. Additionally, these factors can be used to inform future research by determining specific patient risk groups. Ultimately, they can be used to support the development of personalised treatment approaches for anal cancer.

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Acknowledgement

Supported by Cancer Research UK (RadNet grant C19942/A28832).