Ontario
Cancer Care Ontario
Action Cancer Ontario

Evidence-based Series 2-8 Version 2

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Management of Squamous Cell Cancer of the Anal Canal

Members of the Gastrointestinal Cancer Disease Site Group

An assessment conducted in December 2018 deferred the review of Evidence-based Series (EBS) 2-8 Version 2. This means that the document remains current until it is assessed again next year. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)

The reviewed EBS report, which is available on the Gastrointestinal Cancer page consists of the following four sections:

Section 1: Clinical Practice Guideline (ENDORSED)
Section 2: Evidentiary Base
Section 3: EBS Development Methods and External Review Process
Section 4: Guideline Review Summary & Tool

Release Date: February 19th, 2013

For information about this document, the PEBC and/or the most current version of all reports, please visit the CCO web site at http://www.cancercare.on.ca/
or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775 E-mail: ccopgi@mcmaster.ca

PEBC Report Citation (Vancouver Style): Spithoff K, Cummings B, Jonker D, Biagi J; Gastrointestinal Cancer Disease Site Group. Management of squamous cell cancer of the anal canal. Biagi J, Keshavarz, H Toronto (ON): Cancer Care Ontario; 2009 Mar 31 [Endorsed 2013]. Program in Evidence-based Care Evidence-Based Series No.: 2-8 Version 2.

Journal Citation (Vancouver Style): Spithoff K, Cummings B, Jonker D, Biagi JJ; on behalf of the Gastrointestinal Cancer Disease Site Group. Chemoradiotherapy for squamous cell cancer of the anal canal: a systematic review. Clin Oncol. 2014;26(8):473-87.

Guideline Report History

GUIDELINE VERSION	SYSTEMATIC REVIEW		PUBLICATIONS	NOTES AND KEY CHANGES
	Search Dates	Data		
Original version March 2009	1980-2008	Full Report	Web publication	NA
Current Version 2 November 2013	2008- 2013	New data found in Section 4: Document Summary and Review Tool	Updated Web publication	2009 recommendations is **ENDORSED**

Table of Contents

Ontario
Cancer Care Ontario
Action Cancer Ontario

Evidence-Based Series 2-8 Version 2: Section 1

Management of Squamous Cell Cancer of the Anal Canal: Guideline Recommendations

K Spithoff, B Cummings, D Jonker, J Biagi,
and the Gastrointestinal Cancer Disease Site Group

A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Report Date: March 31, 2009

These guideline recommendations have been ENDORSED, which means that the recommendations are still current and relevant for decision making. Please see Section 4: Document Review Summary and Tool for a summary of updated evidence published between 2008 and 2013, and for details on how this Clinical Practice Guideline was ENDORSED.

INTENDED USERS

This guideline is intended for use by clinicians and health care providers involved in the management or referral of adult patients with squamous cell cancer of the anal canal.

QUESTIONS

1. Does the addition of chemotherapy (CT) to radiotherapy (RT) improve outcome for patients with squamous cell cancer of the anal canal?
2. What are the optimal CT drugs for the treatment of patients with squamous cell cancer of the anal canal?
3. Does the use of induction CT before concurrent CT and RT improve outcome for patients with squamous cell cancer of the anal canal?
4. What is the best management for patients with squamous cell cancer of the anal canal who are human immunodeficiency virus (HIV) positive?

Outcomes of interest are colostomy rate, local failure, survival, disease-free survival, acute and late adverse effects, and quality of life.

TARGET POPULATION

These recommendations apply to adult patients (age ≥18 years) with a primary diagnosis of biopsy-proven squamous cell cancer of the anal canal, including basaloid, cloacogenic, and transitional cell tumours. These recommendations do not apply to patients who have previously undergone resection of their tumour. The management of patients who later develop extra-pelvic metastases is not considered in this guideline.

RECOMMENDATIONS

- For all stages of localized squamous cell cancer of the anal canal, concurrent CT and RT is recommended over RT alone to improve local control and decrease colostomy rates.
- The optimal CT drug combination for squamous cell cancer of the anal canal is 5-fluorouracil (5FU) plus mitomycin C (MMC), given concurrently with radiation treatment.
- At this time, induction CT before concurrent CT and RT should be considered an investigational approach.
- It is the expert opinion of the Gastrointestinal Cancer Disease Site Group (GI DSG) that HIV-positive patients with squamous cell cancer of the anal canal should be managed in the same way as patients without known HIV. Treating physicians should be aware that a greater than average risk of toxicity is possible.

QUALIFYING STATEMENTS

- No randomized controlled trials (RCTs) were identified that addressed the management of squamous cell cancer of the anal canal in HIV-positive patients. See the Discussion in Section 2 for a description of non-randomized data available on this topic.
- Only two RCTs included patients with T1 lesions of the anal canal, and results were not reported by disease stage. See the Discussion in Section 2 for further discussion on management of patients with T1N0 disease.
- Two RCTs included patients with squamous cell cancer of the perianal skin. A limited discussion of perianal cancer is included in the Discussion in Section 2.
- James et al. 2013 (ACT II), studied maintenance chemotherapy versus none following chemoradiation and found that maintenance chemotherapy does not improve overall survival or colostomy-free survival. Therefore, maintenance chemotherapy following chemoradiation is not recommended in the management of squamous cell carcinoma of the anal canal. See Section 4 for more details.
- In the trials using MMC in the 5FU-MMC combination regimens, MMC schedules include dose of 12 or 15mg/me day 1 only, and a 10mg/m2 Day 1, 29 dosing. There is no comparative data to allow a recommendation of a preferred schedule.

KEY EVIDENCE

- The United Kingdom Coordinating Committee for Cancer Research (UKCCCR) trial (1) and the European Organisation for Research and Treatment of Cancer (EORTC) trial (2) demonstrated lower rates of colostomy and local failure in patients who received concurrent RT and CT (5FU plus MMC) compared with patients who received RT alone (Section 2, Table 3). Neither trial demonstrated a significant difference in overall survival between treatment arms.
- The Radiation Therapy Oncology Group (RTOG) 87-04 trial (3) demonstrated that the omission of MMC from the standard combination of 5FU plus MMC resulted in a higher colostomy rate (22% versus [vs.] 9%; p=0.002) and local failure rate (34% vs. 16%; p=0.0008) and lower disease-free survival (51% vs. 73%; p=0.0003) at four years, although

overall survival rates were not significantly different. Acute hematologic toxicity rates were significantly lower in the RT plus 5FU alone arm (3% vs. 18%; p<0.001).

- The RTOG 98-11 trial (4) compared the standard RT plus 5FU and MMC approach with concurrent RT plus 5FU and cisplatin, following two courses of induction CT with 5FU and cisplatin. The 5FU and cisplatin combination was associated with a higher colostomy rate at five years (19% vs. 10%; hazard ratio [HR] 1.68; log-rank p=0.02) compared with the standard 5FU and MMC combination. Local failure, overall survival, and disease-free survival were not significantly different between treatment arms. Severe hematologic toxicity rates were lower in the cisplatin arm compared with the MMC arm (42% vs. 61%; p<0.001), but overall acute adverse effects and severe late adverse effects were similar between arms.
- Updated data on RTOG 98-11 shows OS/PFS advantage for 5FU/MMC (Gunderson et al., 2012). See Section 4 for more details.

CLINICAL CONSIDERATIONS

The following issues are beyond the scope of this guideline but warrant consideration in the management of squamous cell cancer of the anal canal. See the Discussion in Section 2 for further discussion of these issues.

- Optimal doses and schedules of RT and CT have not been studied systematically. Readers should refer to Section 2 (Table 1) for details regarding treatment used in the available randomized trials.
- Once patients have completed definitive treatment, regularly scheduled clinical follow-up over a five-year period by an experienced specialist is essential since incomplete response or local recurrence may be amenable to salvage surgery.

Funding

The PEBC is a provincial initiative of Cancer Care Ontario supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent from its funding source.

Contact Information

For further information about this report, please contact:
Dr. Rebecca Wong, Co-Chair, Gastrointestinal Cancer Disease Site Group
Princess Margaret Hospital, University Health Network, Radiation Medicine Program
610 University Avenue, Toronto, Ontario, M5G 2M9
Phone: 416-946-2126; Fax: 416-946-6561,
or

Dr. Jim Biagi, Co-Chair, Gastrointestinal Cancer Disease Site Group
Cancer Centre of Southeastern Ontario, Kingston General Hospital
25 King St W, Kingston, ON, K7L-5P9
Phone: 613-544-2630 ext. 4502; Fax: 613-546-8209

For information about the PEBC and the most current version of all reports, please visit the CCO website at http://www.cancercare.on.ca/ or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775 E-mail: ccopgi@mcmaster.ca

REFERENCES

1. 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;348:1049-54.
2. Bartelink H, Roelofsen F, Eschwege F, Rougier P, Bosset JF, Gonzalez Gonzalez D, 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 European Organization for Research and Treatment of Cancer Radiotherapy and Gastrointestinal Cooperative Groups. J Clin Oncol. 1997;15:2040-9.
3. Flam M, John M, Pajak TF, Petrelli N, Myerson R, Doggett S, et al. Role of mitomycin in combination with fluorouracil and radiotherapy, and of 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;14:2527-39.
4. Ajani JA, Winter KA, Gunderson LL, Pedersen J, Benson AB III, Thomas CR Jr, et al. Fluorouracil, mitomycin, and radiotherapy vs fluorouracil, cisplatin, and radiotherapy for carcinoma of the anal canal: a randomized trial. JAMA. 2008;299:1914-21.

Ontario
Cancer Care Ontario
Action Cancer Ontario

Evidence-Based Series 2-8 Version 2: Section 2

Management of Squamous Cell Cancer of the Anal Canal: Evidentiary Base

K Spithoff, B Cummings, D Jonker, J Biagi,
and the Gastrointestinal Cancer Disease Site Group

A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Report Date: March 31, 2009

These guideline recommendations have been ENDORSED, which means that the recommendations are still current and relevant for decision making. Please see Section 4: Document Review Summary and Tool for a summary of updated evidence published between 2008 and 2013, and for details on how this Clinical Practice Guideline was ENDORSED.

QUESTIONS

1. Does the addition of chemotherapy (CT) to radiotherapy (RT) improve outcome for patients with squamous cell cancer of the anal canal?
2. What are the optimal CT drugs for the treatment of patients with squamous cell cancer of the anal canal?
3. Does the use of induction CT before concurrent CT and RT improve outcome for patients with squamous cell cancer of the anal canal?
4. What is the best management for patients with squamous cell cancer of the anal canal who are human immunodeficiency virus (HIV) positive?

Outcomes of interest are colostomy rate, local failure, survival, disease-free survival, acute and late adverse effects, and quality of life.

INTRODUCTION

Squamous cell carcinoma of the anal canal is an uncommon tumour, representing only 1.5% percent of gastrointestinal tract tumours (1). Incidence of anal canal tumours is

approximately 515 cases per year in Canada, with an age-adjusted annual incidence rate of 1.3 per 100,000 (2); however, analysis of registry data over the last three decades indicates that the incidence of squamous cell cancer of the anus is increasing (3). Due to the rarity of this condition, high-quality clinical trials informing decisions in the treatment of these tumours are few. Since uncertainty exists regarding the optimal treatment of anal canal carcinoma, guidance for Ontario clinicians is needed.

The anal canal extends from the anal verge to the upper border of the anal sphincters, and is approximately 4 to 5 cm in length. The skin for a 5cm radius around the anal verge is called the perianal skin or anal margin. Although several types of tumour histologies can occur in the anal canal, the most common is squamous cell carcinoma, a malignant tumour of the squamous cell epithelia. This type includes cloacogenic, basaloid, and transitional tumours (4). Risk factors for squamous cell carcinoma include human papillomavirus (HPV) infection, immunosuppression (including by HIV), a history of anoreceptive intercourse, and smoking (5).

In population- and referral-based cohort studies, the proportion of patients with anal cancer who have HIV varies between 15-46% (6-11). In these studies, patients with HIV were younger (median ages 42-49 years) than the non-HIV population (median ages 62-63) (6-11). HIV-positive cases were almost all male (90-100%), unlike the non-HIV population (25-42% male) (9-11). The incidence of anal cancer in patients with HIV is increased compared to the general population. In a San Francisco registry of 14,210 adults with HIV from 1990 to 2000, the standardized incidence ratio for anal cancer was 13.4 (12). Increasing use of highly active anti-retroviral therapy (HAART) after 1995 (compared to prior to 1995) did not appear to have reduced the incidence (HR 2.9), or anal cancer mortality (HR 1.4) (12). Another study supported the fact that, since the introduction of HAART, anal cancer incidence in this population group is rising, perhaps simply reflecting longer survival in patients with HIV (13). There is uncertainty whether HIV-positive patients with anal cancer have a decreased tolerance to therapy and worse prognosis than patients without HIV comorbidity.

Until the mid-1970s, anal canal carcinoma was treated most commonly with radical surgery (14); however, this was associated with high rates of morbidity and recurrence of disease. Abdominoperineal resection involves the removal of the anal sphincters and results in a permanent colostomy. With this treatment, five-year survival was between 40% and 70% (1,5). Local or regional node recurrence occurred in 20-50% of patients, usually within two years, and was associated with a poor prognosis. The use of RT and CT for anal canal carcinoma was introduced by Nigro et al. in 1974, initially as neoadjuvant therapy preceding surgical resection (15). With the finding that many patients were rendered free of cancer by preoperative chemoradiotherapy (CRT), both on clinical and histopathological examination, and that local control rates were at least as good as, or better, than those achieved by radical surgery, CRT became a widely accepted definitive therapy option, replacing radical surgery as the primary treatment of choice (16,17). Some case series reports suggested that modern RT could also achieve good control of anal cancer and questioned the need for CT. Persistent or locally recurrent tumours after completion of CT and RT may be amenable to salvage surgery; therefore, close follow-up is considered an important component of care.

Historically, the first CT regimen used with RT was 5-fluorouracil (5FU) and mitomycin C (MMC). Regimens including alternative agents, such as cisplatin, have been proposed and are commonly used, although until recently there has been little evidence to indicate which CT drug combination is optimal in terms of efficacy and safety. Recent studies have also investigated whether the use of induction CT before CRT improves outcome compared with CRT alone.

A search for systematic reviews on squamous cell carcinoma of the anal canal yielded one review by Sato et al published in 2005 (14); however, only MEDLINE was searched for that

review, no quality analysis of the evidence was performed, and new evidence has been published since 2005. The current systematic review was undertaken to develop an up-to-date and comprehensive report on randomized controlled trials (RCTs) comparing CRT with RT alone or comparing different CT options in combination with RT.

METHODS

The evidence-based series (EBS) guidelines developed by Cancer Care Ontario's Program in Evidence-Based Care (PEBC) use the methods of the Practice Guidelines Development Cycle (18). For this project, the core methodology used to develop the evidentiary base was the systematic review. Evidence was selected and reviewed by members of the PEBC GI DSG and methodologists.

The systematic review is a convenient and up-to-date source of the best available evidence on the management of squamous cell cancer of the anal canal. The body of evidence in this review is primarily comprised of mature RCT data. That evidence forms the basis of the recommendations developed by the GI DSG. The systematic review and companion recommendations are intended to promote evidence-based practice in Ontario, Canada. The PEBC is supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent from its funding source.

Literature Search Strategy

A systematic search of the MEDLINE (1980 to June week 4, 2008), EMBASE (1980 to week 27, 2008), and CENTRAL (The Cochrane Library, 2008 Issue 2) was conducted to identify relevant randomized trials meeting the inclusion criteria. In the MEDLINE search, the medical subject heading (MeSH) "exp anus neoplasms" and the text words "anal" or "anus" and "neoplas:", "carcinoma:", "cancer:", or "tumo?r" were combined with intervention-specific terms including the MeSH terms "exp drug therapy", "exp radiotherapy", "exp combined modality therapy", and associated text words. These terms were then combined with a search filter designed to identify randomized trials adapted from a strategy developed by the Scottish Intercollegiate Guidelines Network (SIGN), available at www.sign.ac.uk. Modifications were made to the search terms where appropriate for use in EMBASE. See Appendix 1 for the complete search strategies.

Meeting proceedings of the following organizations were searched from 2003 to 2008 to identify abstract reports or publicly available presentations of relevant RCTs: American Society of Clinical Oncology (ASCO), ASCO Gastrointestinal (GI) Symposium, American Society for Therapeutic Radiology and Oncology (ASTRO), European Society for Therapeutic Radiology and Oncology (ESTRO), European Society for Medical Oncology (ESMO), and European Cancer Conference (ECCO). In addition, reference lists of relevant reviews and included RCTs were screened for additional relevant trials. Experts in the field of medical or radiation oncology for anal canal cancer were contacted to identify any additional trials meeting inclusion criteria.

A search of the National Cancer Institute (NCI) database of ongoing clinical trials (www.cancer.gov) was conducted on July 9, 2008 to identify relevant studies.

Study Selection Criteria

Articles were selected for inclusion if they met all of the following criteria:

1. Fully published reports or abstracts of RCTs (double-blind, single-blind, or open-label).
2. Adult patients (age ≥18 years) with squamous cell cancer of the anal canal were included. Squamous cell tumours include basaloid, cloacogenic, and transitional cell tumours. Studies that included patients with tumours of the anal margin in addition to

patients with tumours of the anal canal were not excluded from this systematic review. Studies that dealt only with squamous cell cancers of the anal margin (perianal skin) were not included.
3. Studies comparing concurrent systemic CT and RT with RT alone or those comparing one or more CT regimens in combination with RT.
4. Studies had to report at least one of the outcomes of interest. The primary outcome measures were colostomy rate and local failure. Secondary outcomes were overall survival, disease-free survival, acute and late adverse effects, and quality of life.

Articles were excluded if they were:
1. Published in a language other than English due to unavailability of translation services.
2. Abstract reports presenting preliminary data only.
3. Reports of RCTs published in the form of letters or editorials.
4. Studies of patients with previous surgical resection of their anal tumour or patients treated for recurrent tumours.

Data Extraction

Two reviewers independently extracted data using a data extraction form. Disagreements regarding extracted data were resolved by consensus.

Synthesizing the Evidence

When clinically homogenous results from two or more trials were available, the data was pooled using the Review Manager software (RevMan 5.0) provided by the Cochrane Collaboration (19). Since hazard ratios (HR), rather than the number of events at a certain time point, are the preferred statistic for pooling time-to-event outcomes (20), those were extracted directly from the most recently reported trial results. The variances of the hazard ratio estimates were calculated from the reported confidence intervals (CI) using the methods described by Parmar et al (20). A random effects model was used for all pooling, as it provides a more conservative estimate of effect (21).

Statistical heterogeneity was calculated using the χ^2 test for heterogeneity and the I^2 percentage. A probability level for the χ^2 statistic less than or equal to 10% ($p \leq 0.10$) and/or an I^2 greater than 50% were considered indicative of statistical heterogeneity. Results are expressed as HR with 95% CI. An HR <1.0 indicates that patients receiving the experimental treatment had a lower probability of experiencing an event; conversely, an HR >1.0 suggests that patients in the control arm experienced a lower probability of an event.

Quality Appraisal of the Evidence

Methodological quality of included trials was independently assessed by two reviewers using the tool described in the Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.0 (22). Assessment of quality items was based on reporting in the trial reports. The method of quality assessment recommended by the Cochrane Collaboration is a domain-based evaluation of sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other sources of bias. Assessment of each domain was comprised of a descriptive summary of how each domain was addressed in the study and the reviewer's judgment as to whether each quality criteria was met. Reviewers rated each study as "Yes" indicating low risk of bias, "No" indicating a high risk of bias, or "Unclear" risk of bias, for each quality domain. Criteria for making judgments about risk of bias were adopted from the Cochrane Collaboration Handbook Version 5.0.0 (22). Disagreements between reviewers were resolved by consensus.

RESULTS

Literature Search Results

The electronic search of the MEDLINE and EMBASE databases yielded a total of 322 unique references. Two reviewers independently scanned titles and abstracts of the retrieved references and 297 were excluded due to ineligibility for study design, study population, comparison, or outcome. The remaining 25 references were retrieved for review of the full publication and were reviewed independently by two reviewers for inclusion. Of the 25 articles reviewed, four met inclusion criteria and were selected for inclusion (23-26). The search of the CENTRAL database by one reviewer yielded 47 references; however, no additional studies that met the inclusion criteria were identified.

One reviewer searched meeting proceedings of the following organizations: ASCO, ASTRO, ECCO, ESTRO, and ESMO. Abstract reports of studies that potentially met the inclusion criteria were discussed with a second reviewer and decisions to include abstracts were reached by consensus, making final agreement 100%. Two abstracts that met inclusion criteria was identified using this method (27,28); however, the trial results reported in the abstracts were subsequently fully published (26). The abstract reports are not discussed further.

Review of reference lists from relevant papers identified an abstract report (29) presenting long-term results of one of the fully published trials (25). This abstract reported only results for subgroup analyses and is not discussed further.

Study Characteristics

Four RCTs were identified that met the inclusion criteria for this review (23-26). Two RCTs compared CRT with RT alone (23,24) and two RCTs compared different CT regimens with RT (25,26). See Table 1 for selected study characteristics. No randomized trials were obtained that addressed the management of anal canal cancer in patients with HIV.

Studies Comparing CRT Versus RT

Two RCTs, the United Kingdom Coordinating Committee for Cancer Research (UKCCCR) trial (23) and the European Organisation for Research and Treatment of Cancer (EORTC) trial by Bartelink et al. (24), were identified that compared concurrent RT plus 5FU and MMC with RT alone. Both trials included patients with tumours of either the anal canal or the anal margin. The UKCCCR trial did not exclude patients with metastatic disease, and 15 patients with distant metastases were included in the analysis. In the UKCCCR trial, more patients in the CRT arm had T4 lesions or palpable nodes compared with patients in the RT-alone arm.

In both trials (23,24), the response to CRT was assessed six weeks after CRT. In the UKCCCR trial, radical surgery was considered for patients with less than 50% response following therapy, while boost RT was recommended for patients with greater than or equal to 50% response or complete remission. Similarly, in the EORTC trial, boost RT was recommended for complete and partial responders, while surgery was advised for patients with progression or no change following initial therapy.

Studies Comparing CRT Versus Other CRT

Two RCTs, the Radiation Therapy Oncology Group (RTOG) 87-04 trial by Flam et al. (25) and the RTOG 98-11 trial by Ajani et al. (26), were identified that compared two different regimens of CRT in patients with anal canal cancer. The 87-04 trial randomized patients to RT plus 5FU and MMC or RT plus 5FU alone, while the 98-11 trial randomized patients to RT plus 5FU and MMC or RT plus 5FU and cisplatin, as induction CT and concurrently with RT. The data safety monitoring board recommended reporting the RTOG 98-11 trial results after the second interim analysis due to determination of futility.

In the RTOG 87-04 study (25), biopsy of the site of the primary tumour was required at four to six weeks after the completion of CRT. If patients had residual disease after initial therapy, salvage RT and CT, comprised of 5FU and either cisplatin or MMC, were administered, provided it was thought there was potential for preservation of anal function. If patients had a positive biopsy six weeks after salvage therapy, surgical resection was recommended. Major compliance problems with RT fields were reported early in the study. In the RTOG 98-11 study (26), patients underwent an optional full-thickness biopsy eight weeks after therapy.

Table 1. Characteristics of included studies.

	UKCCCR (23)	**EORTC Bartelink (24)**	**RTOG 87-04/ ECOG 1289 Flam (25)**	**RTOG 98-11 Ajani (26)**
Comparison	Arm A: RT + 5FU + MMC Arm B: RT	Arm A: RT + 5FU + MMC Arm B: RT	Arm A: RT + 5FU + MMC Arm B: RT + 5FU	Arm A: RT + 5FU + MMC Arm B: RT + 5FU + cisplatin
Accrual period	1987-1994	1987-1994	1988-1991	1998-2005
Year of publication	1996	1997	1996	2008
Sponsorship	UKCCCR (Cancer Research Campaign, Imperial Cancer Research Fund, MRC)	EORTC	NCI	RTOG CCOP NCI
Patient selection criteria	Anal canal or margin Squamous, basaloid, or cloacogenic Any stage excluding T1 tumours suitable for local excision[a].	Anal canal or margin[b] T3-4N0-3 or T1-2N1-3[a] PS 0-1 Age <76 years	Anal canal Epidermoid Any T or N stage[a] KPS ≥ 60	Anal canal Squamous, basaloid or cloacogenic T2-4NanyM0[a] KPS ≥ 60 Age ≥ 18
Patient stratification	Radiotherapy centre	Centre Tumour site	Nodal status, histology, primary tumour size	Gender, clinical N status, tumour diameter
# of patients randomized	585	110	310	682
Median age (range)	Arm A: 63 (26-85) Arm B: 65 (26-88)	NR	Arm A: 62.5 (29-85) Arm B: 59 (26-86)	Arm A: 55 (25-83) Arm B: 55 (31-88)
% male patients	Arm A: 43%, Arm B: 47%	Arm A: 25%, Arm B: 33%	Arm A: 30%, Arm B: 39%	Arm A: 31%, Arm B: 31%
% anal canal patients	75%	NR	100%	100%
Primary outcome	Local failure	NR	NR	DFS
Secondary outcomes	Tumour response Morbidity Survival Cause-specific survival	Overall survival Colostomy-free interval Local control Side effects	Biopsy results Local regional control Time to colostomy Colostomy-free survival DFS OS Toxicity rates	Survival 2-yr colostomy rate Locoregional failure Safety
Chemotherapy regimen	1st course (≥2 hrs before RT): 5FU (CVI) 1000mg/m^2 over 24 hrs d1-4 or 750mg/m^2 over 24 hrs d1-5. MMC (IV bolus) 12 mg/m^2 d1. 2nd course (during final week of RT): 5FU as in 1st course.	5FU 750 mg/m^2 d1-5 (continuous infusion) and d29-33. MMC (IV bolus) 15 mg/m^2 d1.	Arm A: 5FU 1,000 mg/m^2/d 96 hr continuous infusion d1,29. MMC 10 mg/m^2 (IV bolus) d1,29. Arm B: 5FU as in Arm A.	Arm A: 5FU 1,000 mg/m^2 d1-4,29-32 (continuous infusion). MMC 10 mg/m^2 d1,29. Arm B: 5FU 1,000 mg/m^2 d1-4,29-32,57-60,85-88. Cisplatin 75 mg/m^2 d1,29,57,85.
Radiotherapy regimen	45 Gy in 20 or 25 fractions in 4 or 5 weeks	45 Gy in 5 wks, 1.8 Gy daily dose	45 Gy in 5 wks, 1.8 Gy daily dose	Arm A: 45 Gy in 5 wks, 1.8 Gy daily dose Arm B: As above, start d57
Additional radiotherapy (+/- chemotherapy)	Boost RT (15 Gy in 6 fractions or Iridium-192 implant to 25 Gy) recommended for pts with ≥50% response or complete remission at 6 wk after CRT. 419 of 471 pts with good response had boost RT.	Boost RT (electrons, photons or iridium 192 implant) after 6 wk rest period (15 Gy in complete responders, 20 Gy in partial responders).	If residual disease 4 to 6 weeks after CRT, salvage RT (9 Gy in 5 fractions) and CT (5FU as above, cisplatin 100 mg/m^2 6 hr infusion on d2 of RT or substitute MMC 10 mg/m^2 IV bolus if creatinine clearance <50 mL/min). 25 patients received salvage treatment.	If T3, T4, node-positive, or T2 with residual disease after 45Gy, additional RT boost of 10-14 Gy in 2 Gy fractions over 2wks, immediately following initial CRT[c].

	UKCCCR (23)	EORTC Bartelink (24)	RTOG 87-04/ ECOG 1289 Flam (25)	RTOG 98-11 Ajani (26)
Salvage surgery	Radical surgery considered for pts with <50% response. 29 of 43 pts with poor response (65%) had radical surgery.	Surgery advised in case of progression or no change (5 pts in RT arm, none in CRT arm). Non-protocol surgery in 15 pts despite partial or complete remission (9 in RT arm and 6 in CRT arm).	Abdominoperineal resection if positive biopsy 6 wks after salvage CRT.	NR
Median follow-up	42 months	42 months	36 months (42 months for living pts)	30 months
Statistical power calculation	90% power to detect 60% difference in local failure at p=0.05 (2-sided) 6 months after completion of therapy with 130 pts per arm	NR	NR	80% power to detect 10% increase in DFS for cisplatin arm at 5 yrs with 215 events
Baseline characteristic imbalances	More pts in CRT arm had T4 lesions or palpable nodes	None reported	None reported	More pts in cisplatin arm (Arm B) had tumours of both the anal canal and perianal skin
Comments	15 pts with metastatic disease included		Major compliance problem with RT fields early in study.	Data monitoring committee recommended to report results due to futility after 2nd interim analysis

Notes: UKCCCR, United Kingdom Coordinating Committee on Cancer Research; EORTC, European Organization for Research and Treatment of Cancer; RTOG, Radiation Therapy Oncology Group; ECOG, Eastern Cooperative Oncology Group; CCOP, Community Clinical Oncology Program; NCI, National Cancer Institute; MRC, Medical Research Council; 5FU, 5-fluorouracil; MMC, mitomycin C; KPS, Karnofsky Performance Score; PS, performance score; NR, not reported; pts, patients; DFS, disease-free survival; Gy, Gray.
a The UKCCCR and EORTC trials used the 1987 International Union Against Cancer (UICC) staging system (30), the RTOG 87-04 trial used the 1978 UICC staging system (31), and the RTOG 98-11 trial used the American Joint Committee on Cancer (AJCC) staging system (32).
b Histology is stated as "squamous vs. other" in prognostic factor results.
c No information is available on the need for treatment interruptions.

Study Methodological Quality

See Appendix 2 for additional details regarding assessment of methodological quality and Table 2 for a summary. Allocation sequence generation was adequate in all four trials (23-26). Allocation concealment was achieved by central randomization in two trials (23,24) and was not reported for two trials (25,26). None of the included trials reported that patients, health care providers, or outcome assessors were blinded; however, blinding would be difficult in this treatment setting of intravenous CT. All four trials adequately reported reasons for excluding patients from analysis. Details regarding numbers of patients lost to follow-up and excluded from analysis are reported in Appendix 2. None of the included trials appeared to have selective outcome reporting. The EORTC and RTOG 87-04 trials did not report a primary outcome or statistical plan with sample size calculations (24,25); however, both trials were able to detect significant differences between treatment arms for colostomy rate and local recurrence.

Table 2. Summary of methodological quality.

	Adequate sequence generation	Allocation concealment	Blinding	Free of incomplete outcome data	Free of selective outcome reporting	Free of other bias
UKCCCR (23)	☑	☑	☒	☑	☑	☑

EORTC (24)	☑	☑	☒	☑	☑	☑
RTOG 87-04 (25)	☑	**?**	☒	☑	☑	☑
RTOG 98-11 (26)	☑	**?**	☒	☑	☑	☑

Notes: ☑, adequate; ☒, inadequate; ?, unclear.

Outcomes

Colostomy Rate

In all of the trials, the combination of RT plus 5FU and MMC demonstrated a lower colostomy rate than patients who received the alternatives (RT alone, RT plus 5FU alone, RT plus 5FU and cisplatin) (23-26) (Table 3). This difference was statistically significant in three trials (24-26), while colostomy rate was not discussed directly or statistically compared in the UKCCCR trial (23).

Local Failure

Both trials comparing RT plus 5FU and MMC with RT alone demonstrated a significantly lower rate of locoregional failure in patients who received CT (23,24) (Table 3). In the UKCCCR trial, the definition of locoregional failure included residual or recurrent disease, surgery for treatment-related morbidity, and failure to close a pre-treatment colostomy (23). The RTOG 87-04 trial (25) reported a significantly lower local failure rate in patients who received the standard combination of RT with 5FU plus MMC compared with patients who received only 5FU, but no significant difference was reported between RT plus 5FU and MMC and the RT plus 5FU and cisplatin approach at five years in the RTOG 98-11 trial (26).

Overall Survival

None of the four trials demonstrated a significant difference in overall survival between treatment arms (23-26) (Table 3). Meta-analysis of estimated mortality HRs from the two trials comparing RT plus 5FU and MMC with RT alone (23,24) did not demonstrate a significant benefit for the addition of CT (HR, 0.85; 95% CI, 0.67-1.08; p=0.19). No significant statistical heterogeneity between results in the two trials was detected (x^2 =0.09, p=0.77; I^2 = 0%).

Disease-free Survival

Neither of the trials comparing RT plus CT versus RT alone reported disease-free survival data (23,24), although progression-free survival marginally favoured RT plus 5FU and MMC over RT alone in the EORTC trial (log-rank p=0.05) (24) (Table 3). The RTOG 87-04 trial (25) demonstrated a significant benefit in disease-free survival for RT plus 5FU and MMC compared with RT plus 5FU alone while the RTOG 98-11 reported no significant difference in disease-free survival between RT plus 5FU and cisplatin and the standard RT plus 5FU and MMC combination.

Table 3. Efficacy outcomes of included studies.

	Treatment allocation	N	Colostomy rate	Local or locoregional failure	Overall survival	Disease-free survival
UKCCCR (23)	**RT + 5FU + MMC** **RT**	292 285	24%[a] 40%[a]	3-year 39%[b] 61%[b] log-rank p<0.0001 RR=0.54 (95% CI 0.42-0.69)	3-year 65%[c] 58%[c] log rank p=0.25 RR=0.86 (95% CI 0.67-1.11)	NR
EORTC Bartelink (24)	**RT + 5FU + MMC** **RT**	51 52	5-year 28%[d] 60%[d] log rank p=0.002	5-year 32%[b,d,e] 48%[b,d,e] log rank p=0.02	5-year 58%[d] 53%[d] log rank p=0.17	NR[f]
RTOG 87-04/ ECOG 1289 Flam (25)	**RT + 5FU + MMC** **RT + 5FU**	146 145	4-year 9% 22% p=0.002[g]	4-year 16%[h] 34%[h] p=0.0008[g]	4-year 76% 67% p=0.31[g]	4-year 73% 51% p=0.0003[g]
RTOG 98-11 Ajani (26)	**RT + 5FU + MMC** **RT + 5FU + cisplatin**	324 320	5-year 10% 19% log-rank p=0.02 HR=1.68 (95% CI 1.07-2.65)	5-year 25%[b] 33%[b] log rank p=0.07 HR=1.32 (95% CI 0.98-1.78)[i]	5-year 75% 70% log rank p=0.10 HR=1.28 (95% CI 0.90-1.84)[j]	5-year 60% 54% log rank p=0.17 HR=1.20 (95% CI 0.93-1.55)[j]

Notes: N, number of patients evaluated; UKCCCR, United Kingdom Coordinating Committee on Cancer Research; EORTC, European Organisation for Research and Treatment of Cancer; RTOG, Radiation Therapy Oncology Group; ECOG, Eastern Cooperative Oncology Group; 5FU, 5-fluorouracil; MMC, mitomycin M; HR, hazard ratio; CI, confidence interval; RR, relative risk

a Not discussed directly in trial report.

b Locoregional failure.

c Cancer-specific survival: 72% (RT/5FU/MMC) vs. 61% (RT) at three years.

d Estimated from Kaplan-Meier curves.

e Successful surgery for residual disease after RT or CRT was considered "control".

f Progression-free survival (estimated from Kaplan-Meier curves): 60% (RT/5FU/MMC) vs. 42% (RT) at five years (log-rank p=0.05).

g Multivariate Cox proportional hazards model adjusted for nodal status, histology, and primary tumour size.

h Local failure.

i Time to locoregional failure.

j Multivariate Cox proportional hazards model adjusted for sex, clinical nodal status, and tumour diameter.

Acute Adverse Effects

For the comparison of RT plus 5FU and MMC with RT alone, acute adverse effects were significantly greater overall in patients who received CT in the UKCCCR trial (23); however, neither of the two trials reported a significant difference between treatment arms in skin or gastrointestinal toxicity (23,24) (Table 4). Two patients in the UKCCCR trial (23) and one patient in the EORTC trial (24) died as a result of CT and concurrent RT.

In the RTOG 87-04 trial (25) comparing RT plus 5FU with versus without MMC, overall acute adverse effects and hematologic toxicity were significantly higher in the MMC arm. Thrombocytopenia occurred more frequently in the MMC arm; however, there were no significant bleeding complications. Non-hematologic adverse effects were not significantly different between treatment arms.

In the RTOG 98-11 trial (26), severe hematologic toxicity was significantly higher in the MMC arm compared with the cisplatin arm; however, severe non-hematologic and overall acute adverse effects were not significantly different between the treatment arms.

Late Adverse Effects

Late adverse effects more than 60 or 90 days following treatment were not significantly different between treatment arms overall in any of the included trials (Table 4). These effects were not presented by grade in some trials (23-5).

Quality of Life

Quality of life outcomes were not reported for any of the trials included in this review (23-26).

Table 4. Adverse effects reported in included studies.

	Comparison	Acute adverse effects	Late adverse effects
UKCCCR (23)	RT + 5FU + MMC vs. RT	Early morbidity: 47.9% vs. 38.6% (p=0.03) Low WBC: 6.5% vs. 0% Low platelets: 4.8% vs. 0% Overall skin toxicity: 31.8% vs. 27% Severe skin toxicity: 17.1% vs. 13.7% Overall GI toxicity: 15.8% vs. 13.7% Severe GI toxicity: 4.8% vs. 1.8% Overall GU toxicity: 6.8% vs. 4.6% Severe GU toxicity: 1.0% vs. 0.4% 2 deaths attributed to CT	Late morbidity: 41.8% vs. 37.9% (p=0.39) Skin toxicity 20.2% vs. 16.5% GI toxicity 28.8% vs. 27.0% GU toxicity 6.2% vs. 6.7% Other 7.9% vs. 4.9%
EORTC Bartelink (24)	RT + 5FU + MMC vs. RT	Skin toxicity not significantly different Diarrhea not significantly different 1 pt in CRT arm had severe mucosal reaction, diarrhea, bone marrow depression and died of septicemia. Severe diarrhea: 10 pts vs. 4 pts Severe skin reactions: 29 pts vs. 26 pts	Anal damage: Ulcer: 9 pts vs. 2 pts Fistula: 2 pts vs. 3 pts Perforation: 2 pts vs. 2 pts Rectal stenosis requiring surgery: 3 pts vs. 2 pts Skin ulceration: 3 pts vs. 2 pts Severe fibrosis: 3 pts vs. 2 pts Severe toxicity-free interval (early or late): log-rank p=0.21
RTOG 87-04/ ECOG 1289 Flam (25)	RT + 5FU + MMC vs. RT + 5FU	Acute toxicity: 20% vs. 7% (p<0.001) Hematologic: 18% vs. 3% (p<0.001) Non-hematologic: 7% vs. 4% (p=0.63) GI toxicity: not significantly different Skin toxicity: not significantly different Mucous membrane toxicity: not significantly different Thrombocytopenia: more in MMC arm but no significant bleeding complications	Late toxicity: 5% vs. 1% (p=0.26) Grade 4 toxicity (acute or late):23% vs. 7% (p<0.001) Grade 5 toxicity (acute or late): 3% vs. 0.7% (p<0.001)
RTOG 98-11 Ajani (26)	RT + 5FU + MMC vs. RT + 5FU + cisplatin	Severe hematologic: 61% vs. 42% (p<0.001) Severe non-hematologic: 73% vs. 72%(p=0.81) Overall: 86% vs. 81% (p=0.12)	Severe long-term toxicity: 11% vs. 10%

Notes: RT, radiotherapy; 5FU, 5-fluorouracil; MMC, mitomycin C; vs., versus; GI, gastrointestinal; GU, genitourinary; pt(s), patient(s); UKCCCR, United Kingdom Coordinating Committee on Cancer Research; EORTC, European Organisation for Research and Treatment of Cancer; RTOG, Radiation Therapy Oncology Group; ECOG, Eastern Cooperative Oncology Group.

Ongoing Trials

A search of the NCI database (www.cancer.gov) identified three relevant ongoing trials (Table 5). Of these three trials, one is currently recruiting patients, and two are closed but have not yet published results. Once published, the results of these trials will further elucidate the efficacy and safety of alternative CT regimens (5FU and cisplatin concurrent with RT [UKCCCR-ACT-II], MMC plus cisplatin concurrent with RT [EORTC 22011]), the role for induction CT (5FU plus cisplatin [ACCORD-3]), and the role for maintenance adjuvant therapy (5FU plus cisplatin [UKCCCR-ACT-II]).

Table 5. Ongoing randomized trials of anal cancer.

Title	Phase II/III randomized study of radiotherapy with mitomycin and fluorouracil versus mitomycin and cisplatin in patients with locally advanced anal cancer.
Protocol ID:	EORTC 22011, EORTC 40014, NCT00068744
Date last modified:	November 26, 2007
Type of trial:	Randomized, active control
Primary endpoint:	Event-free survival (phase III)
Accrual:	598 patients (299 per arm) will be accrued (phase III)
Sponsorship:	European Organization for Research and Treatment of Cancer (EORTC)
Status:	Ongoing, not recruiting patients
Title	Phase III randomized study of radiotherapy and fluorouracil with either mitomycin or cisplatin and with or without maintenance therapy in patients with primary epidermoid anal cancer.
Protocol ID:	NCRI-ACT-II, EU-20056, ISRCTN26715889, UKCCCR-ACT-II, NCT00025090
Date last modified:	March 18, 2008 (clinicaltrials.gov)
Type of trial:	Randomized, open label, active control
Primary endpoints:	Complete response rate at 6 months, acute toxicity, recurrence-free survival
Accrual:	600 patients (150 per arm) will be accrued
Sponsorship:	Royal Free and University College Medical School
Status:	Recruiting patients
Title:	Phase III randomized study of concurrent chemotherapy and radiotherapy with or without neoadjuvant chemotherapy in patients with locally advanced carcinoma of the anal canal.
Protocol ID:	FNCLCC-FFCD-SFRO-ACCORD-3, EU-98050, NCT00003652
Date last modified:	January 24, 2008
Type of trial:	Randomized, active control
Primary endpoints:	Not reported
Accrual:	350 patients were to be accrued
Sponsorship:	Fédération Nationale des Centres de Lutte Contre le Cancer
Status:	Closed

DISCUSSION

The combination of RT with concurrent CT has been accepted as the preferred initial treatment for squamous cell cancer of the anal canal, without formal comparison with the previous standard of radical surgery, because informal comparisons indicate that survival rates are similar (33), and the majority of patients are spared the need for colostomy.

The organisers of the four trials described have successfully completed multicentre studies of this uncommon cancer (23-26). The trials conducted by the UKCCCR (23) and EORTC (24) have demonstrated that the combination of CT (5FU plus MMC) with RT provides better local control and lower colostomy rates than RT alone. There was no difference in survival rates between the two treatment approaches. This finding is considered to reflect the effectiveness of salvage surgery in a proportion of those with residual or recurrent cancer after initial treatment. The observation of increased hematological toxicity rates in those patients who receive MMC prompted the RTOG 87-04 trial (25). However, it was found that omission of MMC was associated with inferior colostomy-free, local control, and disease-free rates at four years, although the difference in overall survival rates was not significant. In efforts to reduce the rates of local and systemic failure below those seen in the earlier trials, and to examine the role of cisplatin which had been used successfully in the treatment of

squamous cell cancers at other sites, RTOG 98-11 compared RT plus 5FU and MMC as the standard therapy with RT plus 5FU and cisplatin, following two courses of induction 5FU and cisplatin (26). This trial found higher rates of colostomy and local failure in the arm that received the 5FU-cisplatin combination. Disease-free and overall survival rates were not statistically significantly different.

The overall conclusion from this series of trials is that the standard treatment for squamous cell anal canal cancer should be RT coupled with concurrent 5FU and MMC. Induction CT with 5FU and cisplatin was associated with inferior outcome when followed by RT with concurrent 5FU and cisplatin. The doses and schedules of RT and CT, and the techniques by which RT is delivered, have not been studied systematically. Descriptions of late toxicity in the trial publications are limited, and in none of the trials was long term functional outcome reported.

HIV-Positive Patients

The question arises whether the comorbidity of HIV in a patient with anal cancer alters the tolerance to therapy, prognosis, and ultimately the recommended treatment approach. This question has not been addressed in any of the published randomized trials, all of which excluded patients with proven HIV infection; therefore, evidence for the safety and efficacy of therapy in HIV positive patients is limited. Most cohort studies reporting experience treating patients with HIV are small, with a few larger studies including more than 15 patients. These used combined-modality CRT approaches similar to those in non-HIV patients (6,8-11,34-37). Radiation doses ranged from 50.4 to 68.4Gy, including boost (8-11,35-38). CT used was 5FU combined with either MMC or cisplatin. Some studies reported no difference in toxicity and outcome (11,34,36,38). Others reported higher levels of acute toxicity (8-10,35,39) and need for treatment delays and split-course radiotherapy (8,39). Some of these studies suggested interruptions might have had a detrimental impact on local disease control (8,10,36,40) and overall survival (9). Some noted that patients treated with lower CD4 count or high viral loads were more likely to experience toxicity and recommended initiating HAART for a CD4 count less than 200 cells/μL prior to treating the anal cancer (40). Others saw no relationship between CD4 levels and toxicity (8). Whereas overall survival was correlated with CD4 count (35-37,39), most studies did not note any difference in anal cancer specific survival (6,10,37,39) compared to non-HIV patients.

In summary, once optimal medical management is initiated for patients with HIV, it is recommended that the anal canal cancer be managed in the same way as patients without known HIV, with combined modality therapy including CT (5FU and MMC) and RT. Treating physicians should recognize that a greater than average risk of toxicity is possible.

T1N0 Lesions

Randomized trials evaluating treatment for T1N0 lesions are lacking. Although there are non-randomized study reports investigating therapy options for T1N0 lesions in the literature, these have not been systematically assessed in this review. Options from reported literature that result in durable remissions include local excision, radical surgery, RT, or CRT. In an attempt to lessen long-term toxicities of CRT while maintaining high rates of disease control for early-stage disease, investigators have studied therapy of lesser intensity such as abbreviated CRT or RT alone. A surgery-alone treatment, other than local excision with sparing of anal function, is of historic interest only and not a suitable standard of care (41,42). In a recent series of 21 patients from Leeds, United Kingdom (UK), patients with locally excised T1-T2 tumours with a positive or close (<1 mm) margin or microinvasive or T1N0 tumours underwent low-dose CRT. The CRT was limited to 30 Gy external beam RT in 15 fractions and CT (5FU and MMC) in the first week only. At a median follow-up of 42

months, there was only one (4.7% rate) local recurrence that was salvaged with local excision, and a zero incidence of nodal or distant recurrence (43).

Retrospective case series lend support to the use of radiation alone for early-stage disease, by external beam RT, brachytherapy, or both (44-49). In one French series of 57 T1 and 12 Tis patients, three with N1 disease, collected from several centers, patients underwent external beam RT, brachytherapy, or both. Doses of 40–50 Gy were delivered for small-volume disease and 50–60 Gy for T1 lesions. The five-year colostomy-free, overall and disease-free survival rates were 85%, 94%, and 89%, respectively. A 27% late complication rate was reported. All recurrences following RT were amenable to abdominoperineal resection (APR) (48). In a series of 26 patients with T1N0 tumours from a single center, there was a 96% clinical complete response rate to radiation, and local tumour control with sphincter conservation of 81%. The five-year disease-free survival rate for this group was 76% (49).

Of the four randomized trials identified in this review, three used the 1987 International Union Against Cancer (UICC) staging system, in which a T1 tumour is not more than 2cm in size. T1N0 tumours were specifically excluded from the UKCCCR (provided they were suitable for local excision), RTOG 98-11, and EORTC trials (23,24,26). In the UKCCCR trial, approximately 13% of anal canal cancers included were category T1 (23). No results were presented specific to these T1 cancers. The fourth trial, RTOG 87-04, used the 1978 UICC staging system, in which a T1 tumour was less than one third of the circumference or length of the anal canal, and there was no infiltration of the external sphincter muscle. The only outcome reported for the RTOG 87-04 trial specific to early-stage disease was a colostomy-free survival for T1/T2 tumours that was not statistically significantly improved by the addition of MMC.

With inclusion of T1N0 tumours categorised according to current staging systems in one of the randomized trials, and in the absence of stage-specific comparative data from randomized trials, combined modality CT (5FU and MMC) and RT is recommended for T1 lesions that are not suitable for definitive local excision. There is some evidence that T1 cancers may be successfully treated by lower dose RT and CT than that used in the randomised trials. Radiation therapy alone is acceptable to some experts.

Radiotherapy Techniques

Although the optimal RT approach in combination with concurrent CT was not the focus of this review and has not been directly addressed in an RCT, this issue warrants some discussion. RT techniques, dose, fractionation, elective treatment interruptions, and use of brachytherapy versus external beam RT boost vary in clinical trials and in clinical practice. In the UKCCCR, EORTC, and RTOG 87-04 trials (23-25), treatment interruption of approximately six weeks between initial RT and external beam or brachytherapy boost was recommended. In the RTOG 98-11 trial, treatment interruption was not mandated in the protocol and the need for unplanned interruptions was not discussed in the trial report (26).

The technique of split-course RT has been widely adopted in the past to allow resolution of acute toxicity, prevent severe skin reactions, and allow regression of tumour volume following initial external beam RT; however, there is concern that this practice may decrease local tumour control. Data on the impact of length of treatment interruption on treatment efficacy in anal cancer are limited but suggest that shorter overall treatment time is associated with improved outcome. In order to optimize local control rates, individualized treatment breaks as necessary due acute adverse effects may be preferred over planned treatment interruptions (50).

There is no clear evidence in the literature to guide the choice of brachytherapy boost versus external beam boost following initial external beam RT for anal cancer. While

brachytherapy boost allows the application of higher local doses than external beam RT boost and may reduce damage to normal surrounding tissue, it has not been demonstrated in a comparative study that brachytherapy boost improves local control, survival, or toxicity rates over external beam RT boost (51). Of the four available randomized trials, the UKCCCR and EORTC trials allowed either brachytherapy or external beam RT boost (23,24) while the protocols for the RTOG trials did not include brachytherapy boost (25,26).

Recent advances in external beam radiation techniques, such as conformal and highly conformal treatment (e.g., intensity modulated radiation therapy [IMRT]) may result in reduction in acute and long term normal tissue toxicity, but such techniques have not yet been studied systematically or incorporated in randomized trials (52-54). The four randomized trials reported to date employed opposed anterior-posterior field arrangements, or multi-field but non-conformal techniques, for all or most of the treatment. Conformal radiation techniques may reduce the need for interruptions in radiation treatment.

The optimal radiation dose fractionation schedule has not been established. This aspect of treatment was not studied systematically in the randomized trials described earlier. The dose-fractionation-time schedules used in those trials are summarised in Table 1.

Long-term anorectal functional outcomes and late toxicity have not been studied in detail in the randomized trials. Some retrospective studies indicate that function may be impaired in some patients, and/or late toxicity rates may be significant, dependant on the radiation techniques and dose schedules used.

Follow-up

Once patients have completed definitive treatment, follow-up is essential since incomplete response or local recurrence may be amenable to salvage surgery. A systematic review of the evidence on patient follow-up was beyond the scope of this review; however, discussion on this issue is included to provide context to the recommendations. Numerous surgical salvage case series that typically employ APR technique report 40-70% long-term survival (55-60). There is no concrete evidence in the literature to inform a follow-up recommendation, in terms of frequency or duration, nor by which particular specialist. In the RTOG 87-04 trial (25), follow-up consisted of a full-thickness biopsy at four to six weeks to define response and determine further therapy. There was approximately a 10% biopsy-positive rate at this time point, indicating either an early time to treatment failure, false positive as disease may continue to regress over many months, or false negative as some patients with negative biopsies may later fail. In all other trials, biopsies were recommended only when the presence of tumour was suspected. In the UKCCCR trial, follow-up was every two months in the first year, three months the second year, six months through five years, and then annually; it was noted that most treatment failures occurred within 18 months (23). The EORTC trial documented only a follow-up at six weeks after completion of treatment (24). Patients in the RTOG 98-11 trial were re-evaluated at eight weeks following treatment, then every three months for the first year, every six months the second year, then annually (26). This trial allowed optional full-thickness biopsy eight weeks after therapy.

Based on the information available, regularly scheduled clinical follow-up over a five-year period by an experienced specialist is strongly recommended. Biopsy is recommended only when recurrence is suspected. Long term follow-up is also important to detect late radiation effects that might require further management. Salvage surgery should be considered when there is documentation of residual or recurrent disease.

Perianal Cancer

Patients with perianal cancer not suitable for local excision were included in the UKCCCR trial. In the UKCCCR trial, 23% of the patients had tumours classified as arising in the

anal margin (perianal skin) (23). Results were not presented by site of origin of the primary cancer. In the EORTC trial, patients with locally advanced cancers arising in either the anal canal or the anal margin were included, and site of origin of the tumour was a stratification factor (24). The numbers of cancers that arose in each site were not reported. The location of the primary tumour was found to be not prognostically significant for local control or survival (24). As summarised in Table 3, the locoregional failure rates in both trials favoured treatment by combined radiation and 5FU and MMC. Non-randomized series have reported successful management by local excision (where anal sphincter function can be preserved), radical surgery, RT alone and RT combined with CT (61-63). These treatment modalities have not been formally compared, except as noted in the UKCCCR and EORTC trials. The DSG recommends that patients with perianal cancer be managed by the method considered most likely to afford cure with preservation of anorectal function. Where local excision with sparing of the anal sphincters is not possible, RT plus concurrent 5FU and MMC is recommended.

CONCLUSIONS

The standard treatment for adult patients with localized squamous cell cancer of the anal canal should be 5FU and MMC, given concurrently with RT. At this time, induction CT before concurrent CT and RT should be considered an investigational approach. HIV-positive patients with squamous cell cancer of the anal canal should be managed in the same way as patients without known HIV; however, treating physicians should be aware that a greater than average risk of toxicity is possible.

CONFLICT OF INTEREST

Members of the GI DSG involved in the development of this systematic review and practice guideline were polled for potential conflicts of interest. No conflicts were declared.

ACKNOWLEDGEMENTS

The GI DSG would like to thank Drs Bernard Cummings, Jim Biagi, Derek Jonker, and Juhu Kamra and Ms Karen Spithoff for taking the lead in drafting and reviewing this evidence-based series.

For a complete list of the Gastrointestinal Cancer DSG members, please visit the CCO Web site at http://www.cancercare.on.ca/

Funding

The PEBC is a provincial initiative of Cancer Care Ontario supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent from its funding source.

Contact Information

For further information about this report, please contact:
Dr. Rebecca Wong, Co-Chair, Gastrointestinal Cancer Disease Site Group
Princess Margaret Hospital, University Health Network, Radiation Medicine Program
610 University Avenue, Toronto, Ontario, M5G 2M9
Phone: 416-946-2126; Fax: 416-946-6561,
or
Dr. Jim Biagi, Co-Chair, Gastrointestinal Cancer Disease Site Group
Cancer Centre of Southeastern Ontario, Kingston General Hospital
25 King St W, Kingston, ON, K7L-5P9
Phone: 613-544-2630 ext. 4502; Fax: 613-546-8209

For information about the PEBC and the most current version of all reports, please visit the CCO website at http://www.cancercare.on.ca/ or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775 E-mail: ccopgi@mcmaster.ca

REFERENCES

1. Ryan DP, Compton CC, Mayer RJ. Carcinoma of the anal canal. N Eng J Med. 2000;342:792-800.
2. Statistics Canada. Cancer Incidence in Canada 2004 to 2005 [monograph on the Internet]. Ottawa (ON): Statistics Canada; 2007 Jul [cited 2008 Apr 26]. Available from: http://www.statcan.ca/english/freepub/82-231-XIE/82-231-XIE2007001.pdf
3. Ries LAG, Harkins D, Krapcho M, Mariotto A, Miller BA, Feuer EJ, et al. SEER Cancer Statistics Review, 1975-2003. Baltimore, MD: National Cancer Institute; 2005:1-103.
4. Fenger C, Frisch M, Marti AC, Parc C. Tumours of the anal canal. In: Hamilton SR, Aaltonen LA, editors. Pathology and genetics of the digestive system. Lyon, France: IARC Press; 2000:145-55.
5. Uronis HE, Bendell J. Anal cancer: an overview. Oncologist. 2007;12:524-34.
6. Chiao EY, Giordano TP, Richardson P, El-Serag HB. Human immunodeficiency virus-associated squamous cell cancer of the anus: epidemiology and outcomes in the highly active antiretroviral therapy era. J Clin Oncol. 2008;26(3):474-9.
7. Olofinlade O, Adeonigbagbe O, Gualtieri N, Gingold B, Berlin I, Sayeed R, et al. Anal carcinoma: a 15-year retrospective analysis. Scand J Gastroent. 2000;35(11):1194-9.
8. Cohen DC, Cohen KH, Goodgame RW, Paulino AC, Chiao EY. HIV-positive (+) patients on HAART treated with chemoradiation for squamous cell carcinoma of the anus: Efficacy and toxicity compared with HIV-negative (-) patients [abstract on the Internet]. 2008 [cited 2009 Mar 27].2008 ASCO Gastrointestinal Cancers Symposium; Abstract 461. Available from: http://www.asco.org/portal/site/ASCO/menuitem.34d60f5624ba07fd506fe310ee37a01d/?vgnextoid=76f8201eb61a7010VgnVCM100000ed730ad1RCRD&vmview=abst_meeting_categories_view&confID=53
9. Kim JH, Sarani B, Orkin BA, Young HA, White J, Tannebaum I, et al. HIV-positive patients with anal carcinoma have poorer treatment tolerance and outcome than HIV-negative patients. Dis Colon Rectum. 2001;44(10):1496-502.
10. Oehler-Janne C, Huguet F, Provencher S, Seifert B, Negretti L, Riener MO, et al. HIV-specific differences in outcome of squamous cell carcinoma of the anal canal: a multicentric cohort study of HIV-positive patients receiving highly active antiretroviral therapy. J Clin Oncol. 2008;26(15):2550-7.
11. Mathieu N, Aparicio T, Roudot-Thoraval F, Lemarchand N, Bauer P, Hennequin C, et al. Comparison of squamous cell carcinoma of the canal anal (SCCA) prognosis in patients infection or not by human immunodeficiency virus (HIV) [abstract]. J Clin Oncol. 2007;25(18S):4632.
12. Hessol NA, Pipkin S, Schwarcz S, Cress RD, Bacchetti P, Scheer S. The impact of highly active antiretroviral therapy on non-AIDS-defining cancers among adults with AIDS. Am J Epidemiol. 2007;165(10):1143-53.
13. Bower M, Powles T, Newsom-Davis T, Thirlwell C, Stebbing J, Mandalia S, Nelson M, Gazzard B. HIV-associated anal cancer: has highly active anti-retroviral therapy reduced the incidence or improved the outcome? J Acquir Immune Defic Syndr. 2004;37(5):1563-5.
14. Sato H, Koh P, Bartolo DCC. Management of anal canal carcinoma. Dis Colon Rectum. 2005;48:1301-15.
15. Nigro N, Vaitkevicius V, Considine S. Combined therapy for cancer of the anal canal: a preliminary report. Dis Colon Rectum. 1974;17:354-6.

16. Cummings B, Keane T, Thomas G, Harwood A, Rider W, et al. Results and toxicity of the treatment of anal canal carcinoma by radiation therapy or radiation therapy and chemotherapy. Cancer. 1984;54:2062-8.
17. Nigro ND. An evaluation of combined therapy for squamous cell cancer of the anal canal. Dis Colon Rectum. 1984;27:763-6.
18. Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol. 1995;13:502-12.
19. Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions [monograph on the Internet]. Version 5.0.0 [updated 2008 Feb; cited 2009 Mar 27]. The Cochrane Collaboration; 2008. Available from: http://www.cochrane-handbook.org
20. Review Manager (RevMan) [Computer program]. Version 5.0. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration; 2008.
21. Parmar MKB, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Statist Med. 1998;17:2815-34.
22. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7(3):177-88.
23. 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;348:1049-54.
24. Bartelink H, Roelofsen F, Eschwege F, Rougier P, Bosset JF, Gonzalez Gonzalez D, 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 European Organization for Research and Treatment of Cancer Radiotherapy and Gastrointestinal Cooperative Groups. J Clin Oncol. 1997;15:2040-9.
25. Flam M, John M, Pajak TF, Petrelli N, Myerson R, Doggett S, et al. Role of mitomycin in combination with fluorouracil and radiotherapy, and of 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;14:2527-39.
26. Ajani JA, Winter KA, Gunderson LL, Pedersen J, Benson AB III, Thomas CR Jr, et al. Fluorouracil, mitomycin, and radiotherapy vs fluorouracil, cisplatin, and radiotherapy for carcinoma of the anal canal: A randomized trial. JAMA. 2008;299:1914-21.
27. Ajani JA, Winter KA, Gunderson LL, Pedersen J, Benson AB, Thomas C, et al. Intergroup RTOG 98-11: A phase III randomized study of 5-fluorouracil (5-FU), mitomycin, and radiotherapy versus 5-fluorouracil, cisplatin and radiotherapy in carcinoma of the anal canal [abstract]. J Clin Oncol. 2006;24(18S):4009.
28. Gunderson LL, Winter KA, Ajani JA, Pedersen JE, Benson AB, Thomas CR, et al. Intergroup RTOG 9811 phase III comparison of chemoradiation with 5-FU and mitomycin vs 5-FU and cisplatin for anal canal carcinoma: impact on disease-free, overall and colostomy-free survival [abstract]. Int J Radiat Oncol Biol Phys. 2006;66(3 Suppl):43.
29. John M, Flam M, Berkey B, Martenson J, Wasserman T, Russell AH, et al. Five year results and analyses of a phase III randomized RTOG/ECOG chemoradiation protocol for anal cancer [abstract]. ASCO Ann Meet Proc. 1998;17:258a;Abstract 989.
30. Hermanek P, Sobin LH, editors. TN: classification of malignant tumours. 4th ed. Berlin: Springer-Verlag; 1987.
31. Harmer MH, editor. TNM: classification of malignant tumours. 3rd ed. Geneva, Switzerland: International Union Against Cancer; 1978.

32. Beahrs OH, Henson DE, Hutter RVP, Myers MH, editors. AJCC manual for staging of cancer. 3rd ed. Philadelphia (PA): Lippincott; 1988.
33. Myerson RJ, Karnell LH, Menck HR. The National Cancer Data Base report on carcinoma of the anus. Cancer. 1997;80:805-15.
34. Allen-Mersh T, Hanna-Morris AJ, Goldstone SE, Sparano JA, Elrafei T, Bower M. Is chemoradiation the treatment of choice for anal squamous cell carcinoma developing in HIV-positive patients with access to highly active antiretroviral therapy? [abstract] 2004 ASCO Gastrointestinal Cancers Symposium; abstract 233.
35. Edelman S, Johnstone PA. Combined modality therapy for HIV-infected patients with squamous cell carcinoma of the anus: outcomes and toxicities. Int J Rad Oncol Bio Phys. 2006;66(1):206-11.
36. Hwang JM, Rao A, Shieh, Yao J, Tome M. Treatment of HIV positive anal cancer patients with chemoradiation [abstract]. J Clin Oncol. 2006;24(18S):4154.
37. Parthasarathy A, Glaubiger DL, Grant KM, Baron AD. Treatment of anal carcinoma in HIV-positive males: a single institution experience [abstract]. 2006 ASCO Gastrointestinal Cancers Symposium; Abstract 340.
38. Cleator S, Fife K, Nelson M, Gazzard B, Phillips R, Bower M. Treatment of HIV-associated invasive anal cancer with combined chemoradiation. Eur J Cancer. 2000;36(6):754-8.
39. Wexler A, Berson AM, Goldstone SE, Waltzman R, Penzer J, Maisonet OG, et al. Invasive anal squamous-cell carcinoma in the HIV-positive patient: Outcomes in the era of highly active antiretroviral therapy. Dis Colon Rectum. 2008;51(1):73-81.
40. Hoffman R, Welton ML, Klencke B, Weinberg V, Krieg R. The significance of pretreatment CD4 count on the outcome and treatment tolerance of HIV-positive patients with anal cancer. Int J Rad Oncol Bio Phys. 1999;44(1):127-31.
41. Boman BM, Moertel CG, O'Connell MJ, Scott M, Weiland LH, Beart RW, et al. Carcinoma of the anal canal. A clinical and pathologic study of 188 cases. Cancer. 1984;54:114-25.
42. Greenall MJ, Quan SH, Urmacher C, DeCosse JJ. Treatment of epidermoid carcinoma of the anal canal. Surg Gynecol Obstet. 1985;161:509-17.
43. Hatfield P, Cooper R, Sebag-Montefiore D. Involved-field, low-dose chemoradiotherapy for early-stage anal carcinoma. Int J Radiation Oncol Biol Phys. 2008;70:419-24.
44. Schlienger M, Krzisch C, Pene F, Marin JL, Gindrey-Vie B, Mauban S, et al. Epidermoid carcinoma of the anal canal treatment results and prognostic variables in a series of 242 cases. Int J Radiation Oncol Biol Phys. 1989;17:1141-51.
45. Touboul E, Schlienger M, Buffat L, Lefkopoulos D, Pene F, Parc R, et al. Epidermoid carcinoma of the anal canal. Results of curative-intent radiation therapy in a series of 270 patients. Cancer. 1994;73:1569-79.
46. Peiffert D, Bey P, Pernot M, Guillemin F, Luporsi E, Hoffstetter S, et al. Conservative treatment by irradiation of epidermoid cancers of the anal canal: prognostic factors of tumoral control and complications. Int J Radiation Oncol Biol Phys. 1997;37:313-24.
47. Sandhu AP, Symonds RP, Robertson AG, Reed NS, McNee SG, Paul J. Interstitial iridium-192 implantation combined with external radiotherapy in anal cancer: ten years experience. Int J of Radiation Oncol Biol Phys. 1998;40:575-81.
48. Ortholan C, Ramaioli A, Peiffert D, Lusinchi A, Romstaing P, Chauveinc L, et al. Anal canal carcinoma: early-stage tumors < or = 10 mm (T1 or Tis): therapeutic options and original pattern of local failure after radiotherapy. Int J Radiation Oncol Biol Phys. 2005;62:479-85.

49. Deniaud-Alexandre E, Touboul E, Tiret E, Sezeur A, Houry S, Gallot D, et al. Results of definitive irradiation in a series of 305 epidermoid carcinomas of the anal canal. Int J Radiation Oncol Biol Phys. 2003;56:1259-73.
50. Meyer A, Meier zu Eissen J, Karstens JH, Bremer M. Chemoradiotherapy in patients with anal cancer: Impact of length of unplanned treatment interruption on outcome. Acta Oncologica. 2006;45:728-35.
51. Oehler-Janne C, Seifert B, Lutolf UM, Studer G, Glanzmann C, Ciernik F. Clinical outcome after treatment with a brachytherapy boost versus external beam boost for anal carcinoma. Brachytherapy. 2007;6:218-26.
52. Salama JK, Mell LK, Schomas DA, Miller RC, Devisetty K, Jani AB, et al. Concurrent chemotherapy and intensity-modulated radiation therapy for anal canal cancer patients: A multicentre experience. J Clin Oncol. 2007;25:4581-6.
53. Myerson RJ, Garofolo MC, Naqa IE, Abrams RA, Apte A, Bosch WR, et al. Elective clinical target volumes for conformal therapy in anorectal cancer: An RTOG Consensus Panel Contouring Atlas [abstract]. Int J Radiation Oncol Biol Phys. 2008;72(1,Suppl1):156.
54. Vuong T, Kopek N, Duchruet T, Portelance L, Faria S, Bahoric B, et al. Conformal therapy improves the therapeutic index of patients with anal canal cancer treated with combined chemotherapy and external beam radiotherapy. Int J Radiation Oncol Biol Phys. 2007;67:1394-1400.
55. Mullen JT, Rodriguez-Bigas MA, Chang GJ, Barcenas CH, Crane CH, Skibber JM, et al. Results of surgical salvage after failed chemoradiation therapy for epidermoid carcinoma of the anal canal. Ann Surg Oncol. 2007;14:478-83.
56. Pocard M, Tiret E, Nugent K, Dehni N, Parc R. Results of salvage abdominoperineal resection for anal cancer after radiotherapy. Dis Colon Rectum. 1998;41:1488-93.
57. Allal AS, Laurencet FM, Reymond MA, Kurtz JM, Marti MC. Effectiveness of surgical salvage therapy for patients with locally uncontrolled anal carcinoma after sphincter-conserving treatment. Cancer. 1999;86:405-9.
58. Klas JV, Rothenberger DA, Wong WD, Madoff RD. Malignant tumors of the anal canal: the spectrum of disease, treatment, and outcomes. Cancer. 1999;85:1686-93.
59. Longo WE, Vernava AM 3rd, Wade TP, Coplin MA, Virgo KS, Johnson FE. Recurrent squamous cell carcinoma of the anal canal. Predictions of initial treatment failure and results of salvage therapy. Ann Surg. 1994;220:40-9.
60. Schiller DE, Cummings BJ, Rai S, Le LW, Last L, Davey P, et al. Outcomes of salvage surgery for squamous cell carcinoma of the anal canal. Ann Surg Oncol. 2007;14:2780-9.
61. Klas JV, Rothenberger DA, Wong WD, et al. Malignant tumors of the anal canal. The spectrum of disease, treatment and outcomes. Cancer. 1999;85:1686.
62. Newlin HE, Zlotecki RA, Morris CG, et al. Squamous cell cancer of the anal margin. J Surg Oncol. 2004;86:55.
63. Bieri S, Allal AS, Kurtz JM. Sphincter-conserving treatment of carcinomas of the anal margin. Acta Oncol. 2001;40:29.

Appendix 1. Search Strategies

MEDLINE

1. exp anus neoplasms/
2. ((neoplas: or carcinoma: or cancer: or tumo?r:) adj3 (anal or anus)).mp.
3. or/1-2
4. exp drug therapy/
5. exp radiotherapy/
6. exp combined modality therapy/
7. (chemotherapy or radiotherapy or radiation or chemoradi: or irradiation).mp.
8. (mitomycin or cisplat: or 5FU or 5-FU or fluorouracil).mp.
9. or/4-8
10. 3 and 9
11. Randomized controlled trials as topic/
12. randomized controlled trial.pt.
13. random allocation/
14. double blind method/
15. single blind method/
16. clinical trial.pt.
17. exp clinical trials as topic/
18. or/11-17
19. (clinic: adj trial$1).tw.
20. ((singl: or doubl: or treb: or tripl:) adj (blind$3 or mask$3)).tw.
21. placebos/
22. placebo:.tw.
23. randomly allocated.tw.
24. ((allocat: or assign:) adj2 random:).tw.
25. or/19-24
26. 18 or 25
27. case report:.tw,pt.
28. (letter or editorial or comment).pt.
29. (historical article or news).pt.
30. or/27-29
31. 26 not 30
32. 10 and 31
33. (198: or 199: or 2:).ed.
34. 32 and 33

EMBASE

1. exp anus tumor/
2. ((neoplasm: or carcinoma or cancer) adj3 (anal or anus)).mp.
3. or/1-2
4. exp drug therapy/
5. exp radiotherapy/
6. multimodality cancer therapy/
7. (chemotherapy or radiotherapy or radiation or chemoradi: or irradiation).mp.
8. (mitomycin or cisplat: or 5FU or 5-FU or fluorouracil).mp.
9. or/4-8
10. 3 and 9
11. clinical trial/

12. randomized controlled trial/
13. randomization/
14. single blind procedure/
15. double blind procedure/
16. crossover procedure/
17. placebo/
18. randomi?ed controlled trial:.tw.
19. rct.tw.
20. random allocation.tw.
21. randomly allocated.tw.
22. allocated randomly.tw.
23. (allocated adj2 random).tw.
24. single blind:.tw.
25. double blind:.tw.
26. ((treble or triple) adj blind:).tw.
27. placebo:.tw.
28. prospective study/
29. or/11-28
30. case study/
31. case report.tw.
32. abstract report/ or letter/
33. or/30-32
34. 29 not 33
35. 10 and 34

CENTRAL

1. (anal or anus) in record title
2. (cancer or carcinoma or neoplasm: or tumo:) in record title
3. 1 and 2

Meeting Proceedings

1. “anal” or “anus” in record title

Appendix 2. Methodological quality assessment.

	UKCCCR (23)	EORTC Bartelink (24)	RTOG 87-04 / ECOG 1289 Flam (25)	RTOG 98-11 Ajani (26)
Sequence generation	Blocked allocation	Pocock minimization technique	Randomization scheme derived by Zelen	Zelen permuted block method
Allocation concealment	Central randomization by telephone	Central randomization by telephone or email	NR	NR
Blinding	None reported	None reported	None reported	No
Incomplete outcome data	All analyses were on an intention-to-treat basis, excluding 8 ineligible pts for whom local failure could not be measured (7 not epidermoid cancer, 1 previous anorectal excision). 9 pts (2 RT, 7 CRT) excluded from logrank analyses because no follow-up data received. 4 pts subsequently lost to follow-up and censored at time of last follow-up.	7 randomized pts were ineligible (3 inadequate staging, 2 poor physical condition, 2 prior treatment for anal cancer, 1 no data). No pts lost to follow-up evaluation. Reported analyses based on eligible pts. A separate analysis of all randomized pts on an intention-to-treat basis reached similar conclusions.	19 randomized pts excluded from all analyses (7 inadequate data, 4 no measurable disease, 4 metastatic disease, 4 no reason given). 2-year data incomplete for 24 pts.	38 randomized pts not analyzed (23 ineligible, 5 withdrew consent, 2 no baseline information, 8 no follow-up data). Analyses by intention-to-treat, excluding pts who were ineligible, withdrew consent, or had inadequate data.
Selective outcome reporting	No	No	No	No
Other sources of bias	None identified	None identified	None identified	None identified

Notes: NR, not reported; pts, patients; UKCCCR, United Kingdom Coordinating Committee on Cancer Research; EORTC, European Organisation for Research and Treatment of Cancer; RTOG, Radiation Therapy Oncology Group; ECOG, Eastern Cooperative Oncology Group.

Evidence-Based Series 2-8 Version 2: Section 3

Management of Squamous Cell Cancer of the Anal Canal: EBS Development Methods and External Review Process

K Spithoff, B Cummings, D Jonker, J Biagi,
and the Gastrointestinal Cancer Disease Site Group

A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Report Date: March 31, 2009

These guideline recommendations have been ENDORSED, which means that the recommendations are still current and relevant for decision making. Please see Section 4: Document Review Summary and Tool for a summary of updated evidence published between 2008 and 2013, and for details on how this Clinical Practice Guideline was ENDORSED.

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO) (1). The PEBC mandate is to improve the lives of Ontarians affected by cancer, through the development, dissemination, implementation, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care.

The PEBC supports a network of disease-specific panels, termed Disease Site Groups (DSGs) and Guideline Development Groups (GDGs), as well as other groups or panels called together for a specific topic, all mandated to develop the PEBC products. These panels are comprised of clinicians, other health care providers and decision makers, methodologists, and community representatives from across the province.

The PEBC is well known for producing evidence-based guidelines, known as Evidence-based Series (EBS) reports, using the methods of the Practice Guidelines Development Cycle (1,2). The EBS report consists of an evidentiary base (typically a systematic review), an interpretation of and consensus agreement on that evidence by our groups or panels, the resulting recommendations, and an external review by Ontario clinicians and other stakeholders in the province for whom the topic is relevant. The PEBC has a formal

standardized process to ensure the currency of each document, through the periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original guideline information.

The Evidence-Based Series

Each EBS is comprised of three sections:

- *Section 1: Guideline Recommendations*. Contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the group or panel involved and a formalized external review in Ontario by review participants.
- *Section 2: Evidentiary Base*. Presents the comprehensive evidentiary/systematic review of the clinical and scientific research on the topic and the conclusions reached by the group or panel.
- *Section 3: EBS Development Methods and External Review Process*. Summarizes the evidence-based series development process and the results of the formal external review of the draft version of Section 1: Guideline Recommendations and Section 2: Evidentiary Base.

DEVELOPMENT OF THIS EVIDENCE-BASED SERIES

Development and Internal Review

This EBS was developed by the GI DSG of the CCO PEBC. The series is a convenient and up-to-date source of the best available evidence on the management of squamous cell cancer of the anal canal, developed through review of the evidentiary base, evidence synthesis, and input from external review participants in Ontario. The GI DSG is comprised of medical oncologists, radiation oncologists, and surgeons. The GI DSG reviewed the evidence identified by the authors and consensus was reached regarding the recommendations.

Report Approval Panel

Prior to the submission of the EBS draft report for external review, the report was reviewed and approved by the PEBC Report Approval Panel, which consists of three members, including an oncologist, with expertise in clinical and methodology issues. Key issues raised by the Report Approval Panel included:

- Clinical and contextual issues raised in the Discussion section could be mentioned briefly in Section 1 under a new heading such as “Other Considerations”.
- It should be clarified how many reviewers performed the quality appraisal of the evidence and how disagreements were resolved.
- In the draft Target Population (Section 1), the authors indicate that the recommendations do not apply to those who have undergone resection of their tumour according to surgical oncologic principles. The authors should clarify if there are competing treatment options available for the population included in this guideline or a subset of these patients.
- There should be a disclaimer added to the discussion of radiotherapy techniques and patient follow-up to indicate that these discussions are not based on systematic review but are provided as context, as these topics are beyond the scope of this document.
- The discussion of HIV positive patients and T1N0 tumours deal with generalizability of the guideline results. The default position should be that recommendations apply to subsets unless there are compelling data to indicate otherwise. The HIV recommendations appear well justified; however, the T1N0 discussion leads to a potential alternative recommendation. The authors should clarify whether a

systematic process was used to assemble the data for these discussions or whether such a process was beyond the scope of this document.

- Two of the trials do not appear to have an explicit primary outcome or a statistical plan with sample size calculation. While this does not necessarily result in diminished study quality, the authors should comment on risks for deficiencies and the statistical power of the two trials.
- The reason for not pooling the results of the UK, EORTC, and RTOG 87-04 trials has not been sufficiently justified. The authors should consider pooling these data as a difference in overall survival might be detected. Such an observation could provide an additional level of importance to the final recommendations.

Modifications and Responses to Report Approval Panel Comments

The following modifications and responses were made to address key issues raised by the Report Approval Panel:

- Brief statements on clinical and contextual issues addressed in the Discussion section were added under a new heading in Section 1 call "Clinical Considerations".
- It was clarified under the Methods heading that study quality appraisal was performed by two reviewers, with disagreements resolved by consensus.
- The phrase "according to surgical oncological principles" was removed from the statement in the Target Population that the recommendations do not apply to patients who have undergone surgical resection of their tumour.
- Disclaimers were added to Section 1 and the Discussion in Section 2 to clarify that the data radiotherapy techniques, patient follow-up, and management of T1N0 tumours were not collected systematically. Review of non-randomized evidence for these issues was beyond the scope of this document and these issues are discussed for context only.
- A sentence was added to Section 2 to indicate that two trial reports did not specify a primary outcome or sample size calculation.
- The Gastrointestinal DSG did not consider the pooling of the RTOG 87-04 trial comparing RT with 5FU/MMC vs. 5FU alone with the two trials comparing CRT vs. RT alone to be appropriate. Survival data from the UK and EORTC trials were pooled; however, the hazard ratio estimate was statistically non-significant. The pooled mortality hazard ratio was added to the text of the Results section.

External Review by Ontario Clinicians

The PEBC external review process is two-pronged and includes a targeted peer review that is intended to obtain direct feedback on the draft report from a small number of specified content experts and a professional consultation that is intended to facilitate dissemination of the final guidance report to Ontario practitioners.

Following the review and discussion of Section 1: Guideline Recommendations and Section 2: Evidentiary Base of this EBS and the review and approval of the report by the PEBC Report Approval Panel, the GI DSG circulated Sections 1 and 2 to external review participants for review and feedback. Box 1 summarizes the draft recommendations and supporting evidence developed by the GI DSG.

BOX 1:
DRAFT RECOMMENDATIONS (approved for external review December 15, 2008)

- For all stages of localized squamous cell cancer of the anal canal, concurrent CT and RT is recommended over RT alone to improve local control and decrease colostomy rates.

- The optimal CT drug combination for squamous cell cancer of the anal canal is 5-fluorouracil (5FU) plus mitomycin C (MMC), given concurrently with radiation treatment.
- At this time, induction CT before concurrent CT and RT should be considered an investigational approach.
- It is the expert opinion of the Gastrointestinal Cancer Disease Site Group (GI DSG) that HIV-positive patients with squamous cell cancer of the anal canal should be managed in the same way as patients without known HIV. Treating physicians should be aware that a greater than average risk of toxicity is possible.

QUALIFYING STATEMENTS

- No randomized trials were identified that addressed the management of squamous cell cancer of the anal canal in HIV-positive patients. See the Discussion in Section 2 for a description of non-randomized data available on this topic.
- Only two randomized controlled trials (RCTs) have included patients with T1 lesions of the anal canal, and results are not reported by disease stage. See the Discussion in Section 2 for further discussion on management of patients with T1N0 disease.

Methods

Targeted Peer Review: During the guideline development process, 10 targeted peer reviewers from Ontario or Canada considered to be clinical and/or methodological experts on the topic were identified by the working group. One of the reviewers identified by the working group suggested a colleague from outside of Canada who should be considered for inclusion in the targeted review process. Several weeks prior to completion of the draft report, the nominees were contacted by email and asked to serve as reviewers. Five reviewers agreed and the draft report, and a questionnaire were sent via email for their review. The questionnaire consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a guideline. Written comments were invited. The questionnaire and draft document were sent out from January 9 to 15, 2009. Follow-up reminders were sent at two weeks (email) and at four weeks (telephone call). The Gastrointestinal DSG reviewed the results of the survey.

Professional Consultation: Feedback was obtained through a brief online survey of health care professionals who are the intended users of the guideline. Gastrointestinal medical oncologists, radiation oncologists, and surgeons from Ontario in the PEBC database were contacted by email to inform them of the survey. Participants were asked to rate the overall quality of the guideline (Section 1) and whether they would use and/or recommend it. Written comments were invited. Participants were contacted by email and directed to the survey website where they were provided with access to the survey, the guideline recommendations (Section 1) and the evidentiary base (Section 2). The notification email was sent on January 22, 2009. The consultation period ended on February 15, 2009. The Gastrointestinal DSG reviewed the results of the survey.

Results

Targeted Peer Review: Five responses were received from five reviewers. Key results of the feedback survey are summarized in Table 6.

Table 6. Responses to nine items on the targeted peer reviewer questionnaire.

Question	Lowest Quality (1)	(2)	(3)	(4)	(5)	(6)	Highest Quality (7)
1. Rate the guideline development methods.					2	2	1
2. Rate the guideline presentation.					1	3	1
3. Rate the guideline recommendations.				1		2	2
4. Rate the completeness of reporting.			1			3	1
5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?			1			2	1
6. Rate the overall quality of the guideline report.				1		3	1
	Strongly Disagree (1)	(2)	(3)	(4)	(5)	(6)	Strongly Agree (7)
7. I would make use of this guideline in my professional decisions.			1			2	2
8. I would recommend this guideline for use in practice.		1				2	2
9. What are the barriers or enablers to the implementation of this guideline report? Responses are compiled in the comments section below.							

Summary of Written Comments

The main points contained in the written comments were:

Guideline development methods

- Two reviewers commented favourably on the guideline development methods. One reviewer commented that including only literature published in English limits the guideline.

Guideline presentation

- Three reviewers commented that the review was very well written and organized.

Completeness of reporting

- One reviewer commented that reporting was complete.
- The literature review finishes in June 2008 and misses one important oral presentation in September 2008 at ESTRO (report of a French trial on induction and boost RT dose variation) that impacts the recommendations (3). The trial showed no difference either by induction CT or higher boost RT dose. T he results are equivalent or superior to the MMC arm of the RTOG 98-11 study (4).

- The Introduction section should refer to data from Scotland, Denmark, and the US showing a doubling of anal cancer incidence in the last 15 years (6,7).
- The Discussion section states that survival rates are similar between radical resection and primary CRT, making reference to a study by Myerson et al (19). This should be corrected to state that survival rates are either similar or superior with CRT.
- One reviewer suggested that the authors include additional references on HIV positive patients (8), RT techniques (9-12), and toxicity for pelvic RT (13). Five additional references were also suggested for inclusion (14-18).
- Two reviewers suggested including additional information on RT techniques such as intensity-modulated radiation therapy (IMRT) and conformal therapy.
- One reviewer suggested the addition of a sentence indicating that the ACCORD-3 trial together with the CALGB 9281 are not showing any benefits for induction CT, prior to CRT for advanced lesions.

Guideline recommendations

- One reviewer commented that the recommendations were clear and simple. A second reviewer commented that while some recommendations are accurate, others are arbitrary and do not reflect the literature or the lack of literature.
- One reviewer suggested that the authors should wait for the published results from the ACCORD-3 trial and/or the UK ACT-II trial to make any comments regarding cisplatin and MMC. Alternatively, a suggestion was made to add a qualifying statement such as: "Results of ACT-II will give us a better understanding of the difference in outcomes between cisplatin and MMC" (5). The recommendation should be that at the present time in the North American context, RT with 5FU/MMC seems superior to 5FU/cisplatin in terms of colostomy free survival only but this is at the price of higher toxicity.
- One reviewer commented that, while HIV-positive patients can be treated with combined CRT, the specific regimen cannot be defined whether it is 5FU/MMC or 5FU/cisplatin or whether the dose of both CT and RT should be reduced. It should be mentioned that the optimal regimen is yet to be defined for those patients. Management should be kept to teams with relatively large volume of patients because of the higher toxicity.
- One reviewer commented that a note on dose response should be included in the text such as, "The North-American standard is likely 54 Gy and the European standard is 60 Gy to gross volume and at this point in time there is no benefit to go beyond 65 Gy for advanced lesions (> 5 cm) for local control." A note on the possibility of a lesser dose for HIV patients (around 50 Gy to gross disease) may be appropriate.
- One reviewer commented that T1NO patients were excluded from four of the phase III trials of combined CRT, and the recent article by Ajani (14) showed a relationship between tumour size and outcomes irrespective of the CT regimen. The toxicity is likely to be greater, there is no known benefit in terms of survival, and most of these patients were excluded from CRT and are still treated by RT alone. The current conclusion regarding management of T1N0 patients does not reflect the literature. It would be more appropriate to state that either RT alone or CRT are valid alternatives and the treatment should be individualized and that there is no data suggesting CRT should be the standard. The comment in the Discussion that patients with contraindications to RT or CT should be managed following discussion in a multidisciplinary team should be removed.
- One reviewer requested a recommendation on dose and number of chemotherapy cycles for early stage tumours (T1).

- One reviewer commented that guidance on management of patients who develop metastatic disease would be helpful.

Barriers or enablers to the implementation of this guideline report

- Two reviewers commented that there are no barriers to implementation. One of the reviewers commented that the guidelines reflect current practice and are not controversial.

General comments

- One reviewer commented that the guidelines should be used across the country.

Professional Consultation: Seven responses were received. Key results of the feedback survey are summarized in Table 7.

Table 7. Responses to four items on the professional consultation survey.

General Questions: Overall Guideline Assessment	Lowest Quality (1)	(2)	(3)	(4)	(5)	(6)	Highest Quality (7)
1. Rate the overall quality of the guideline report.					2	3	2
	Strongly Disagree (1)	(2)	(3)	(4)	(5)	(6)	Strongly Agree (7)
2. I would make use of this guideline in my professional decisions.					1	4	2
3. I would recommend this guideline for use in practice.					2	3	2
4. What are the barriers or enablers to the implementation of this guideline report? Responses are compiled in the comments section below.							

Summary of Written Comments

The main points contained in the written comments were:

- Four responders indicated that there are no barriers to implementation of this guideline report, and one responder commented that the recommendations reflect current standard of practice.
- One responder indicated that most patients are likely referred to a cancer centre because cancer of the anal canal is an uncommon malignancy requiring specialist care. In contrast, another responder indicated that most patients are referred to general surgeons and familiarization of the guideline contents should be directed at general surgeons to ensure that patients are sent for appropriate therapy.
- One responder comments that the guideline report was a well-structured review.
- Two responders commented on the recommendations regarding treatment of HIV positive patients. One responder commented that the guideline recommendation to give the same treatment despite CD4 counts was contrary to the responder's current understanding and the guideline, if approved, would provide evidence to treat such patients with CRT despite low CD4 counts. The second responder stated that the

section on HIV positive patients should not be included in the guideline since the summarised suggestion is limited by poor quality retrospective data.

- One responder commented that the guideline is too generalized and does not address particular group of patients (e.g., transitional zone cancer and cancer involving anal skin and anal verge). The data on which this guideline is based are very limited, likely reflecting the lower incidence of anal cancer.

Modifications/Responses

As a result of the feedback received from the Targeted Review and Professional Consultation processes, the following responses were made by the authors:

- The original literature search cut-off date of June 2008 was maintained. The abstract report of the ACCORD-3 trial presented at ESTRO in September 2008 is not clear and lacks sufficient detail.
- The authors did not feel that it was necessary to reference anal cancer incidence data from Scotland, Denmark, and the United States. The Introduction in Section 2 provides epidemiologic data, including increase in incidence.
- The authors did not agree with the reviewers' interpretation that the study by Myerson et al (19) demonstrates similar *or superior* survival results for CRT compared with radical surgery. The study demonstrated similar outcomes between treatment groups and the range of outcomes in comparisons of non-randomized studies is wide.
- Additional references suggested for inclusion by one reviewer were reviewed and included in the Discussion of Section 2 where appropriate.
- Commentary on the radiation techniques of conformal therapy and IMRT was added to the Discussion in Section 2.
- Additional information was added to the Ongoing Trials section in Section 2 to show the questions that each of the ongoing trials will answer. The authors did not feel that it was practical to wait for the results of these trials to be published before making recommendations on cisplatin and MMC or induction therapy.
- The authors did not feel that there was evidence to support the reviewer's suggestion that management of HIV-positive patients be limited to teams with relatively large volume of patients. Volume-related outcomes were beyond the scope of this review.
- RT doses are not standard but depend on physician preference. A sentence was added to refer readers to the summary Table 1 for the RT schedules used in the randomized trials. The authors did not feel that the addition of a statement on the possibility of a lesser dose for HIV-positive patients was necessary or supported by strong evidence.
- The wording of the final paragraph under the heading "T1N0 lesions" in the Discussion of Section 2 was modified to state that there is some evidence to support lower doses of RT and CT for T1 lesions than those given in randomized trials and that some experts consider RT alone to be adequate. The comment that patients with contraindications to RT or CT should be managed following discussion in a multidisciplinary team was removed.
- The Target Population in Section 1 was modified to state that the management of patients who later develop extra-pelvic metastases is not addressed in this guideline.
- A brief paragraph on perianal cancer was added to the Discussion in Section 2.
- The authors did not feel that additional discussion on whether 5FU/cisplatin or reduced doses would be indicated for HIV-positive patients was necessary.

Conclusion

This EBS report reflects the integration of feedback obtained through the external review process with final approval given by the GI DSG and the Report Approval Panel of the PEBC. Updates of the report will be conducted as new evidence informing the question of interest emerges.

For a complete list of the Gastrointestinal Cancer Disease Site Group members, please visit the CCO website at: https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/gastrointestinal

Funding

The PEBC is a provincial initiative of Cancer Care Ontario supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent from its funding source.

Contact Information

For further information about this report, please contact:
Dr. Rebecca Wong, Co-Chair, Gastrointestinal Cancer Disease Site Group
Princess Margaret Hospital, University Health Network, Radiation Medicine Program
610 University Avenue, Toronto, Ontario, M5G 2M9
Phone: 416-946-2126; Fax: 416-946-6561,
or
Dr. Jim Biagi, Co-Chair, Gastrointestinal Cancer Disease Site Group
Cancer Centre of Southeastern Ontario, Kingston General Hospital
25 King St W, Kingston, ON, K7L-5P9
Phone: 613-544-2630 ext. 4502; Fax: 613-546-8209

For information about the PEBC and the most current version of all reports, please visit the CCO website at http://www.cancercare.on.ca/ or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775 E-mail: ccopgi@mcmaster.ca

REFERENCES

1. Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol. 1995;13:502-12.
2. Browman GP, Newman TE, Mohide EA, Graham ID, Levine MN, Pritchard KI, et al. Progress of clinical oncology guidelines development using the practice guidelines development cycle: the role of practitioner feedback. J Clin Oncol. 1998;16(3):1226-31.
3. Peiffert D, Gerard JP, Ducreux M, Lemanski C, Francois E, Giovannini M, et al. Induction chemotherapy (ICT) and dose intensification of the radiation boost in locally advanced anal canal carcinoma (LAACC): definitive analysis of the intergroup ACCORD 03 trial (Fédération Nationale des Centres de Lutte Contre le Cancer Fondation Française des Cancerologie Digestive) [abstract]. Radiother Oncol. 2008:88(Suppl 2):S20.
4. Ajani JA, Winter KA, Gunderson LL, Pedersen J, Benson AB III, Thomas CR Jr, et al. Fluorouracil, mitomycin, and radiotherapy vs fluorouracil, cisplatin, and radiotherapy for carcinoma of the anal canal: A randomized trial. JAMA. 2008;299:1914-21.
5. James R, Meadows H, Wan S. ACT II: the second UK phase III Anal Cancer Trial. Clin Oncol. 2005;17:364-6.
6. Brewster DH, Bhatti LA. Increasing incidence of squamous cell carcinoma of the anus in Scotland 1975-2002. Br J Cancer. 2006;95:87-90.
7. 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;101:281-8.
8. Oehler-Janne C, Huguet F, Provencher S, Seifert B, Negretti L, Riener M, et al. HIV-specific differences in outcome of squamous cell carcinoma of the anal canal: A multicentric cohort study of HIV-positive patients receiving highly active antiretroviral therapy. J Clin Oncol. 2008;26:2550-7.
9. Salama JK, Mell LK, Schomas DA, Miller RC, Devisetty K, Jani AB, et al. Concurrent chemotherapy and intensity-modulated radiation therapy for anal canal cancer patients: A multicentre experience. J Clin Oncol. 2007;25:4581-6.
10. Myerson RJ, Garofolo MC, Naqa IE, Abrams RA, Apte A, Bosch WR, et al. Elective clinical target volumes for conformal therapy in anorectal cancer: an RTOG Consensus Panel Contouring Atlas [abstract]. Int J Radiation Oncol Biol Phys. 2008;72(1,Suppl 1):156.
11. Saarilahti K, Arponen P, Vaalavirta L, Tenhunen M. The effect of intensity-modulated radiotherapy and high dose rate brachytherapy on acute and late radiotherapy-related adverse events following chemoradiotherapy of anal cancer. Radiother Oncol. 2008;87:383-90.
12. Vuong T, Kopek N, Duchruet T, Portelance L, Faria S, Bahoric B, et al. Conformal therapy improves the therapeutic index of patients with anal canal cancer treated with combined chemotherapy and external beam radiotherapy. Int J Radiation Oncol Biol Phys. 2007;67:1394-1400.
13. Baxter NN, Habermann EB, Tepper JE, Durham SB, Virnig BA. Risk of pelvic fractures in older women following pelvic irradiation. JAMA. 2005;294:2587-93.
14. Ajani JA, Winter KA, Gunderson LL, Pedersen J, Benson AB III, Thomas CR Jr, et al. US Intergroup Anal Carcinoma Trial: Tumor diameter predicts for colostomy. J Clin Oncol. E-published ahead of print 2009 Jan 12. DOI: 10.1200/JCO.2008.19.6857.
15. Charnley N, Choudhury A, Chesser P, Cooper RA, Sebag-Montefiore D. Effective treatment of anal cancer in the elderly with low-dose chemoradiotherapy. Br J Cancer. 2005;92:1221-5.

16. Das P, Crane CH, Ajani JA. Current treatment for localized anal carcinoma. Curr Opinion Oncol. 2007;19:396-400.
17. Meropol NJ, Niedzwiecki D, Shank B, Colacchio TA, Ellerton J, Valone F, et al. Induction therapy for poor-prognosis anal canal carcinoma: A phase II study of the Cancer and Leukemia Group B (CALGB 9281). J Clin Oncol. 2008;26:3229-34.
18. Clark MA, Hartley A, Geh JI. Cancer of the anal canal. Lancet Oncol. 2004;5:149-57.
19. Myerson RJ, Karnell LH, Menck HR. The National Cancer Data Base report on carcinoma of the anus. Cancer. 1997;80:805-15.

Evidence-Based Series #2-8 version 2: Section 4

A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Management of Squamous Cell Cancer of the Anal Canal

Guideline Review Summary

Biagi J, Keshavarz H, and the Gastroinstestinal Cancer Disease Site Group

Review Date: September 19, 2013

The March 2009 guideline recommendations are
ENDORSED
This means that the recommendations are still current and relevant for decision making.

OVERVIEW

Evidence-based Series History

This guidance document was originally released by the Program in Evidence-Based Care, Cancer Care Ontario, in March 2003. In June 2013, the PEBC guideline update strategy was applied, and the new updated document released in February 2014. The Summary and the Full Report in this version are the same as in the June 2003 version, with the exception of a description of the new evidence and an impact statement, both below.

Update Strategy

Using the Document Assessment and Review Tool at the end of this report, the PEBC update strategy includes an updated search of the literature, review and interpretation of the new eligible evidence by clinical experts from the authoring guideline panel, and consideration of the guideline and its recommendations in response to the new available evidence.

DOCUMENT ASSESSMENT AND REVIEW RESULTS

Questions Considered

1. Does the addition of chemotherapy (CT) to radiotherapy (RT) improve outcome for patients with SCC of the anal canal?

2. What are the optimal CT drugs for the treatment of patients with squamous cell cancer of the anal canal?

3. Does the use of induction CT before concurrent CT and RT improve outcomes for patients with squamous cell cancer of the anal canal?

4. What is the best management for patients with SCC of the anal canal who are HIV positive?

Literature Search and New Evidence

The new search (2008 to June 2013) yielded five relevant new publications. Brief results of these publications are shown in the Document Review Tool at the end of this report .

Impact on Guidelines and Its Recommendations

The new data supports the existing recommendations. However, evidence on the strategy of maintenance chemotherapy was not available at the time of first publication. Subsequently, James et al. 2013 (ACT II), studied maintenance chemotherapy versus none following chemoradiation and found that maintenance chemotherapy does not improve overall survival or colostomy-free survival. Therefore, maintenance chemotherapy following chemoradiation is not recommended in the management of squamous cell carcinoma of the anal canal. In addition, updated data on RTOG 98-11 shows OS/PFS advantage for 5FU/MMC (Gunderson et al., 2012).This long tem follow up confirming survival advantage validates the recommendation of 5FU plus MMC.

Hence, the Gastrointestinal Cancer DSG **ENDORSE** the 2009 recommendations.

Number and title of document under review	2-8: Management of Squamous Cell Cancer of the Anal Canal
Current Report Date	March 31, 2009
Clinical Expert	Jim Biagi
Research Coordinator	Homa Keshavarz
Date Assessed	November 27th, 2012
Approval Date and Review Outcome (once completed)	ENDORSED

Original Question(s):

1. Does the addition of chemotherapy (CT) to radiotherapy (RT) improve outcome for patients with SCC of the anal canal?

2. What are the optimal CT drugs for the treatment of patients with squamous cell cancer of the anal canal?

3. Does the use of induction CT before concurrent CT and RT improve outcomes for patients with squamous cell cancer of the anal canal?

4. What is the best management for patients with SCC of the anal canal who are HIV positive?

Target Population:

Adult patients (≥18 years) with a primary diagnosis of biopsy-proven squamous cell cancer of the anal canal, including basaloid, cloacogenic and transitional cell tumours.

Study Section Criteria:

Inclusion Criteria:

1. Fully published reports or abstracts of RCTs (double or single blind, or open label).
2. Adult patients (≥18 years) with SCC of the anal canal, including basaloid, cloacogenic and transitional cell tumours. Studies that included patients with tumours of the anal margin in addition to patients with tumours of the anal canal were not excluded. Studies that dealt only with SCC of the anal margin (perianal skin) were not included.
3. Studies comparing concurrent systemic CT and RT with RT alone or those comparing one or more CT regimens in combination with RT.
4. Studies had to report at least one outcome of interest. Primary outcomes were colostomy rates and local failure. Secondary outcomes were OS, DFS, acute and late AEs and QOL.

Exclusion Criteria:

1. Published in a language other than English.
2. Abstracts presenting only preliminary data.
3. Reports of RCTs published in the form of letters or editorials.
4. Studies of patients with previous surgical resection of their anal tumour or patients treated for recurrent tumours.

Updated Search Details:

- MEDLINE – July 2008 to June 2013
- EMBASE – 2008 to June 2013
- ASCO, ASCO GI – 2009-2013 (Annual Meeting and GI Symposium). 69 abstracts were reviewed but none were included

Brief Summary/Discussion of New Evidence:
There were 54 hits in MEDLINE, 17 hits in EMBASE and 54 hits from ASCO/ASCO GI conferences. Of these 4 were deemed eligible that comprised of 1 abstract, 2 fully published RCTs and 1 QOL paper from an included RCT. There was also one relevant systematic review but the inclusion criteria stipulate the inclusion of RCTs only.

Table of evidence – efficacy outcomes

Trial	Treatment allocation	N	Colostomy rate	Local or locoregional failure	Overall survival	Disease-free survival
UKCCCR/ACT 1 Northover 2010	RT + 5FU + MMC RT	292 285	24%[a] 40%[a]	3-year 29.7%[b] 53.4%[b] HR = 0.46 (95% CI – 0.35-0.60); p<0.001	3-year 64.6%[c] 60.00%[c] HR 0.86 (0.70-1.04), p = 0.12	NR
ACCORD 03 Peiffert 2012	Induction CT + CRT CRT alone	150 157	NR	NR	5-year 74.5% 71% p=0.81	NR
EORTC Bartelink, 1997	RT + 5FU + MMC RT	51 52	5-year 28%[d] 60%[d] log rank p=0.002	5-year 32%[b,d,e] 48%[b,d,e] log rank p=0.02	5-year 58%[d] 53%[d] log rank p=0.17	NR[f]
RTOG* 98-11 Ajani, 2008	RT + 5FU + MMC RT + 5FU + cisplatin	324 320	5-year 10% 19% log-rank p=0.02 HR=1.68 (95% CI 1.07-2.65)	5-year 25%[b] 33%[b] log rank p=0.07 HR=1.32 (95% CI 0.98-1.78)[i]	5-year 75% 70% log rank p=0.10 HR=1.28 (95% CI 0.90-1.84)[j]	5-year 60% 54% log rank p=0.17 HR=1.20 (95% CI 0.93-1.55)[j]
RTOG* 98-11 update Gunderson 2011	RT/5FU/MMC RT/5FU/cisplatin	325 324	5-year 12% 17% p=0.074	5-year 20% 26% p=0.087	5-year 78% 71% log rank p=0.026	5-year 68% 58% log rank p=0.006
ACT II James, 2013	RT/5FU/MMC RT/5FU/cisplatin RT/5FU/MMC + maintenance 5FU/cisplatin RT/5FU/cisplatin + maintenance 5FU/cisplatin	246 246 226 222	23%[k] 26%[k] 23%[k] 22%[k]	NR	5-year Cisplatin: 77% MMC: 79% HR=1.05 (95% CI 0.80-1.38) Maintenance: 76% No maintenance: 79% HR=1.07 (95% CI 0.81-1.41)	NR[l]

*note: long term follow-up data of RTOG 98-11
N, number of patients evaluated; UKCCCR, United Kingdom Coordinating Committee on Cancer Research; EORTC, European Organisation for Research and Treatment of Cancer; RTOG, Radiation Therapy Oncology Group; ECOG, Eastern Cooperative Oncology Group; 5FU, 5-fluorouracil; MMC, mitomycin M; HR, hazard ratio; CI, confidence interval; RR, relative risk

[a] Not discussed directly in trial report.
[b] Locoregional failure.

[c] Cancer-specific survival: 72% (RT/5FU/MMC) vs. 61% (RT) at three years.
[d] Estimated from Kaplan-Meier curves.
[e] Successful surgery for residual disease after RT or CRT was considered "control".
[f] Progression-free survival (estimated from Kaplan-Meier curves): 60% (RT/5FU/MMC) vs. 42% (RT) at five years (log-rank p=0.05).
[g] Multivariate Cox proportional hazards model adjusted for nodal status, histology, and primary tumour size.
[h] Local failure.
[i] Time to locoregional failure.
[j] Multivariate Cox proportional hazards model adjusted for sex, clinical nodal status, and tumour diameter.
[k] Post-treatment colostomy plus pre-treatment colostomy not reversed within 8 months from start of treatment.
[l] 5-year PFS: MMC 69% vs. cisplatin 69%; maintenance 70% vs. no maintenance 69%.

Table of evidence - adverse effects

Trial	Comparison	Acute adverse effects	Late adverse effects
UKCCCR/ACT 1 Northover 2008	RT + 5FU + MMC vs. RT	Early morbidity: 47.9% vs. 38.6% (p=0.03) Low WBC: 6.5% vs. 0% Low platelets: 4.8% vs. 0% Overall skin toxicity: 31.8% vs. 27% Severe skin toxicity: 17.1% vs. 13.7% Overall GI toxicity: 15.8% vs. 13.7% Severe GI toxicity: 4.8% vs. 1.8% Overall GU toxicity: 6.8% vs. 4.6% Severe GU toxicity: 1.0% vs. 0.4% 2 deaths attributed to CT	Late morbidity: 41.8% vs. 37.9% (p=0.39) Skin toxicity 20.2% vs. 16.5% GI toxicity 28.8% vs. 27.0% GU toxicity 6.2% vs. 6.7% Other 7.9% vs. 4.9%
RTOG 98-11 Ajani/Gunderson 2011	RT + 5FU + MMC vs. RT + 5FU + cisplatin	Severe hematologic: 61% vs. 42% (p<0.001) Severe non-hematologic: 73% vs. 72%(p=0.81) Overall: 86% vs. 81% (p=0.12)	Severe long-term toxicity: 11% vs. 10%
ACCORD 03 Peiffert 2012	Induction CT + CRT CRT alone	Not reported by treatment group.	Not reported by treatment group.
EORTC Bartelink 1997	RT + 5FU + MMC vs. RT	Skin toxicity not significantly different Diarrhea not significantly different 1 pt in CRT arm had severe mucosal reaction, diarrhea, bone marrow depression and died of septicemia. Severe diarrhea: 10 pts vs. 4 pts Severe skin reactions: 28 pts vs. 26 pts	Anal damage: Ulcer: 9 pts vs. 2 pts Fistula: 2 pts vs. 3 pts Perforation: 2 pts vs. 2 pts Rectal stenosis requiring surgery: 3 pts vs. 2 pts Skin ulceration: 3 pts vs. 2 pts Severe fibrosis: 3 pts vs. 4 pts Severe toxicity-free interval (early or late): log-rank p=0.21
RTOG 87-04/ ECOG 1289 Flam,1996	RT + 5FU + MMC vs. RT + 5FU	Acute toxicity: 20% vs. 7% (p<0.001) Acude Hematologic: 18% vs. 3% (p<0.001) Acude Non-hematologic: 7% vs. 4% (p=0.63) GI toxicity: not significantly different Skin toxicity: not significantly different Mucous membrane toxicity: not significantly different Thrombocytopenia: more in MMC arm but no significant bleeding complications	Late toxicity: 5% vs. 1% (p=0.26) Grade 4 toxicity (acute or late): 23% vs. 7% (p<0.001) Grade 5 toxicity (acute or late): 3% vs. 0.7% (p<0.001)
ACT II James, 2013	RT/5FU/MMC vs. RT/5FU/cisplatin	*During CRT (n=940)* Severe non-hematologic: 62% vs. 68% Severe hematologic: 26% vs. 16% Any severe toxic effect: 71% vs. 72% *During maintenance therapy (n=448)* Severe non-hematologic: 14% vs. 15% Severe hematologic: 4% vs. 3% Any severe toxic effect: 17% vs. 18%	NR

Quality of Life - An analysis of preliminary quality of life data for the ACCORD 03 trial reported significant improvement in emotional function, global health status, insomnia, constipation, appetite loss, pain and intestinal function two months after treatment compared with pre-treatment scores (Tournier-Rangeard 2008).

New References Identified:

1. Tournier-Rangeard L, Mercier M, Peiffert D, Gerard JP, Romestaing P, Lemanski C, et al. Radiochemotherapy of locally advanced anal canal carcinoma: prospective assessment of early impact on the quality of life (randomized trial ACCORD 03). Radiotherapy & Oncology 2008;87(3):391-7.

2. Northover J, Glynne-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). British Journal of Cancer 2010;102(7):1123-8.

3. Gunderson LL, Winter KA, Ajani JA, Pedersen JE, Moughan J, Benson AB, 3rd, et al. Long-term update of US GI intergroup RTOG 98-11 phase III trial for anal carcinoma: survival, relapse, and colostomy failure with concurrent chemoradiation involving fluorouracil/mitomycin versus fluorouracil/cisplatin. Journal of Clinical Oncology 2012;30(35):4344-51.

4. Peiffert D, Tournier-Rangeard L, Gerard JP, Lemanski C, Francois E, Giovannini M, et al. Induction chemotherapy and dose intensification of the radiation boost in locally advanced anal canal carcinoma: final analysis of the randomized UNICANCER ACCORD 03 trial. Journal of Clinical Oncology 2012;30(16):1941-8.

5. James RD, Glynne-Jones R, Meadows HM, Cunningham D, Myint AS, Saunders MP, et al. Mitomycin or cisplatin chemoradiation with or without maintenance chemotherapy for treatment of squamous-cell carcinoma of the anus (ACT II): a randomised, phase 3, open-label, 2x2 factorial trial. Lancet Oncology 2013;14(6):516-24.

Clinical Expert Interest Declaration:
JB declared no conflicts of interest.

Instructions. For each document, please respond YES or NO to all the questions below. Provide an explanation of each answer as necessary.

1. Does any of the newly identified evidence, on initial review, contradict the current recommendations, such that the current recommendations may cause harm or lead to unnecessary or improper treatment if followed?	No
2. On initial review, a. Does the newly identified evidence support the existing recommendations? b. Do the current recommendations cover all relevant subjects addressed by the evidence, such that no new recommendations are necessary?	a.Yes b. No. While the recommendations are upheld by the new evidence, an additional finding from James et al supports that we include a statement about maintenance chemotherapy: in a 2x2 factorial design, maintenance chemotherapy versus none was studied, with the conclusion that maintenance chemotherapy does not add to OS or colo-FS and therefore cannot be recommended.

3. Is there a good reason (e.g., new stronger evidence will be published soon, changes to current recommendations are trivial or address very limited situations) to postpone updating the guideline? Answer Yes or No, and explain if necessary:	No
4. Do the PEBC and the DSG/GDG responsible for this document have the resources available to write a full update of this document within the next year?	N/A

Review Outcome	ENDORSED
DSG/GDG Approval Date	November 3rd, 2013
DSG/GDG Commentary	

Literature Search Strategy: June 2013 Update

MEDLINE

1. exp anus neoplasms/
2. ((neoplas: or carcinoma: or cancer: or tumo?r:) adj3 (anal or anus)).mp.
3. or/1-2
4. exp drug therapy/
5. exp radiotherapy/
6. exp combined modality therapy/
7. (chemotherapy or radiotherapy or radiation or chemoradi: or irradiation).mp.
8. (mitomycin or cisplat: or 5FU or 5-FU or fluorouracil).mp.
9. or/4-8
10. 3 and 9
11. Meta-Analysis as topic/
12. meta analy$.tw.
13. metaanaly$.tw.
14. meta analysis.pt.
15. (systematic adj (review$1 or overview$1)).tw.
16. exp Review Literature as topic/
17. or/11-16
18. cochrane.ab.
19. embase.ab.
20. medline.ab.
21. pubmed.ab.
22. (psychlit or psyclit).ab.
23. (psychinfo or psycinfo).ab.
24. (cinahl or cinhal).ab.
25. science citation index.ab.
26. bids.ab.
27. cancerlit.ab.
28. or/18-27
29. reference list$.ab.
30. bibliograph$.ab.
31. hand-search$.ab.
32. relevant journals.ab.
33. manual search$.ab.
34. or/29-33
35. selection criteria.ab.
36. data extraction.ab.
37. 35 or 36
38. review.pt.
39. 37 and 38
40. comment.pt.
41. letter.pt.
42. editorial.pt.
43. animal/
44. human/
45. 43 not (43 and 44)
46. or/40-42,45

47. 17 or 28 or 34 or 39
48. 47 not 46
49. Randomized controlled trials as topic/
50. randomized controlled trial.pt.
51. random allocation/
52. Double blind method/
53. Single blind method/
54. clinical trial.pt.
55. exp clinical trials as topic/
56. or/49-55
57. (clinic$ adj trial$1).tw.
58. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.
59. Placebos/
60. Placebo$.tw.
61. Randomly allocated.tw.
62. (allocated adj2 random).tw.
63. random:.tw.
64. or/57-63
65. 56 or 64
66. Case report.tw.
67. Letter.pt.
68. Historical article.pt.
69. or/66-68
70. 65 not 69
71. 70 or 48
72. 10 and 71
73. (200806: or 200807: or 200808: or 200809: or 20081: or 2009: or 201:).ed.
74. 2013:.dc.
75. 73 or 74
76. 72 and 75

EMBASE

1. exp anus tumor/
2. ((neoplasm: or carcinoma or cancer) adj3 (anal or anus)).mp.
3. or/1-2
4. exp drug therapy/
5. exp radiotherapy/
6. multimodality cancer therapy/
7. (chemotherapy or radiotherapy or radiation or chemoradi: or irradiation).mp.
8. (mitomycin or cisplat: or 5FU or 5-FU or fluorouracil).mp.
9. or/4-8
10. 3 and 9
11. exp Meta Analysis/
12. ((meta adj analy$) or metaanalys$).tw.
13. (systematic adj (review$1 or overview$1)).tw.
14. or/11-13
15. cancerlit.ab.
16. cochrane.ab.

17. embase.ab.
18. (psychlit or psyclit).ab.
19. (psychinfo or psycinfo).ab.
20. (cinahl or cinhal).ab.
21. science citation index.ab.
22. bids.ab.
23. or/15-22
24. reference lists.ab.
25. bibliograph$.ab.
26. hand-search$.ab.
27. manual search$.ab.
28. relevant journals.ab.
29. or/24-28
30. data extraction.ab.
31. selection criteria.ab.
32. 30 or 31
33. review.pt.
34. 32 and 33
35. letter.pt.
36. editorial.pt.
37. animal/
38. human/
39. 37 not (37 and 38)
40. or/35-36,39
41. 14 or 23 or 29 or 34
42. 41 not 40
43. clinical trial/
44. randomized controlled trial/
45. randomization/
46. single blind procedure/
47. double blind procedure/
48. crossover procedure/
49. placebo/
50. randomi?ed controlled trial$.tw.
51. rct.tw.
52. random allocation.tw.
53. randomly allocated.tw.
54. allocated randomly.tw.
55. (allocated adj2 random).tw.
56. single blind$.tw.
57. double blind$.tw.
58. ((treble or triple) adj blind$).tw.
59. placebo$.tw.
60. Prospective study/
61. or/43-60
62. Case study/
63. case report.tw.
64. abstract report/ or letter/
65. or/62-64
66. 61 not 65

67. 10 and 66
68. (2008: or 2009: or 201:).ew.
69. 67 and 68

ASCO Meeting Proceedings:

In title: anal or anus

OUTCOMES DEFINITIONS

1. ARCHIVED – An archived document is a document that will no longer be tracked or updated but may still be useful for academic or other informational purposes. The document is moved to a separate section of the Web site and each page is watermarked with the phrase "ARCHIVED".

2. ENDORSED – An endorsed document is a document that the DSG/GDG has reviewed for currency and relevance and determined to be still useful as guidance for clinical decision making. A document may be endorsed because the DSG/GDG feels the current recommendations and evidence are sufficient, or it may be endorsed after a literature search uncovers no evidence that would alter the recommendations in any important way.

3. DELAY – A Delay means that there is reason to believe new, important evidence will be released within the next year that should be considered before taking further action.

4. UPDATE – An Update means that the DSG/GDG recognizes that there is new evidence that makes changes to the existing recommendations in the guideline necessary but these changes are more involved and significant than can be accomplished through the Document Assessment and Review process. The DSG/GDG will rewrite the guideline at the earliest opportunity to reflect this new evidence. Until that time, the document will still be available as its existing recommendations are still of some use in clinical decision making.