Institution: University of Leeds

Unit of Assessment: UoA 1

Title of case study: A paradigm shift in radiotherapy treatment delivery to reduce toxicity and improve cancer outcome for patients with squamous cell cancer of the anus

Period when the underpinning research was undertaken: 2003-2014

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
David Sebag-Montefiore	Professor of Clinical Oncology and Hon Consultant	2012- present
	Consultant Clinical Oncology and Hon Prof	2010-2012
	Consultant Clinical Oncology and Hon Senior Lecturer	1995-2010

Period when the claimed impact occurred: 2013-present

Is this case study continued from a case study submitted in 2014? No

1. Summary of the impact (indicative maximum 100 words)

Anal cancer is diagnosed in around 4,300 (European) and 8,600 (United States) patients per year, with incidence rising by 3% per year. Radiotherapy-based treatment is the standard of care. Research led by Sebag-Montefiore has improved radiotherapy techniques in the curative treatment of anal cancer. It determined the radiotherapy schedule used in the largest global anal cancer trial (ACT2), that then translated into routine clinical practice in the UK and internationally. His subsequent research introduced intensity modulated radiotherapy, a complex novel radiotherapy schedule resulting in substantial patient and overall socio-economic benefit. This technique significantly reduced treatment toxicity, improved compliance with treatment, and resulted in 94% one-year survival. In the English NHS, its population-based use in anal cancer patients increased from 13% in 2013 to 74% in 2018. The success of this treatment approach has led to numerous recommendations in national and international cancer guidelines.

2. Underpinning research (indicative maximum 500 words)

Sebag-Montefiore is an internationally leading clinical academic whose anal cancer research has delivered a paradigm shift in use of chemoradiotherapy (CRT) for anal cancer as primary treatment. Progressive optimisation of the radiotherapy technique has resulted in a progressive and substantial reduction in the acute side effects of treatment, avoidance of interruptions in radiotherapy and delivery of the planned dose of radiotherapy and chemotherapy, resulting in higher rates of successful locoregional treatment and overall survival.

Before 1994, surgery was the standard of care for anal cancer patients. A pivotal phase 3 trial (ACT1) including 585 patients, conducted between 1988 and 1994, demonstrated that CRT was a more effective primary treatment than radiotherapy, with surgery necessary only in recurrent or persistent disease. This resulted in CRT replacing surgery as the new standard of care as initial curative treatment for anal cancer patients [**1**].

Novel shrinking field radiotherapy - In 2003, Sebag-Montefiore published a new radiotherapy technique [**2**]**.** This continuous “shrinking field” technique using a 50Gy radiotherapy dose resulted in 30% grade 3/4 acute toxicity, 94% of patients completing the full radiotherapy course and locoregional control in 78% patients. The results from this single centre study were substantially

better than the ACT1 trial that used a crude radiotherapy technique, higher dose (60Gy) and resulted in 71% grade 3/4 toxicity.

ACT2 trial shrinking field radiotherapy - Sebag-Montefiore co-led ACT2, the largest global phase III randomised anal cancer trial, funded by Cancer Research UK (CRUK). This UK wide trial utilised Sebag-Montefiore's "shrinking field" radiotherapy technique. 940 patients were recruited between 2000 and 2008**.** Its results showed effectiveness of fluorouracil and mitomycin with radiotherapy (50Gy) in 28 daily fractions and confirmed that this protocol should remain national standard of care for anal cancer patients [**3**].

Intensity modulated radiotherapy - Sebag-Montefiore led a national group to further improve radiotherapy treatment delivery in preparation for future anal cancer trials to optimise radiotherapy dose. This research utilises advances in radiotherapy dosimetry, computational hardware and software to create an intensity modulated radiotherapy treatment (IMRT) technique for anal cancer patients. The development of this technique is complex, where all pelvic lymph node regions as well as the primary tumour are to be treated and represented a substantial challenge. IMRT delivers multiple beams or arcs of radiation that include modulation of the components of the radiotherapy beam intensity to allow complex beam shaping and the delivery of different doses of radiation to gross tumour and areas of microscopic nodal disease. This results in significantly greater sparing of the normal tissues including the skin, genital structures, bowel and bladder. The UK anal cancer IMRT technique was published in 2014 and made available online at www.analimrtguidance.co.uk [**4**].

3. References to the research (indicative maximum of six references)

1. Northover J, Glynne-Jones R, **Sebag-Montefiore D**, James R, Meadows H, Wan S, Jitlal M, Ledermann J. Chemoradiation for the treatment of epidermoid anal cancer: 13-year follow-up of the first randomised UKCCCR Anal Cancer Trial (ACTI). *Br J Cancer*. 2010;102(7):1123-8. DOI: 10.1038/sj.bjc.6605605

2. Melcher AA, **Sebag-Montefiore D**. Concurrent chemoradiotherapy for squamous cell carcinoma of the anus using a shrinking field radiotherapy technique without a boost. *Br J Cancer*. 2003;88(9):1352-7. DOI: 10.1038/sj.bjc.6600913

3. James RD, Glynne-Jones R, Meadows HM, Cunningham D, Myint AS, Saunders MP, Maughan T, McDonald A, Essapen S, Leslie M, Falk S, Wilson C, Gollins S, Begum R, Ledermann J, Kadalayil L, **Sebag-Montefiore D**. 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, 2 × 2 factorial trial. *Lancet Oncol*. 2013;14(6):516-24. DOI: 10.1016/S1470-2045(13)70086-X

4. Muirhead R, Adams RA, Gilbert DC, Glynne-Jones R, Harrison M, **Sebag-Montefiore D**, Hawkins MA. Anal cancer: developing an intensity-modulated radiotherapy solution for ACT2 fractionation. *Clin Oncol (R Coll Radiol)*. 2014;26(11):720-1. DOI: 10.1016/j.clon.2014.08.001

4. Details of the impact (indicative maximum 750 words)

Anal cancer is diagnosed in over 4,300 patients per year in Europe and 8,600 in the United States and its incidence has increased by 75% in the last three decades. It is predominantly a pelvic disease with a relatively low rate of metastases, where successful local treatment to eradicate the disease and to prevent recurrence is of crucial importance to achieve long-term survival. The progressive improvement in radiotherapy technique, influenced by the findings from Sebag-Montefiore's research, has led to substantial patient benefit by reducing severe acute treatment-related side effects, avoiding interruption in radiotherapy, ensuring the full dose delivery of radiotherapy and chemotherapy, resulting in high rates of locoregional control and overall survival.

The shrinking field radiotherapy approach was used in the Cancer Research UK ACT2 trial co-led by Sebag-Montefiore. It is the largest global phase III randomised anal cancer trial and recruited 940 patients between 2000 and 2008. 75% of patients completed planned radiotherapy and delays in treatment of 7 or more days occurred in 15% of patients. 3-year progression free survival was 71% and overall survival 83%, compared with 65% overall survival in ACT1. In 94/940 patients a delay in overall treatment beyond 42 days resulted in 78% 3-year overall survival.

As anal cancer is relatively uncommon and in the absence of detailed treatment guidelines, centres in the UK and internationally used the ACT2 radiotherapy protocol in their routine clinical practice and this remained the standard treatment approach for more than a decade.

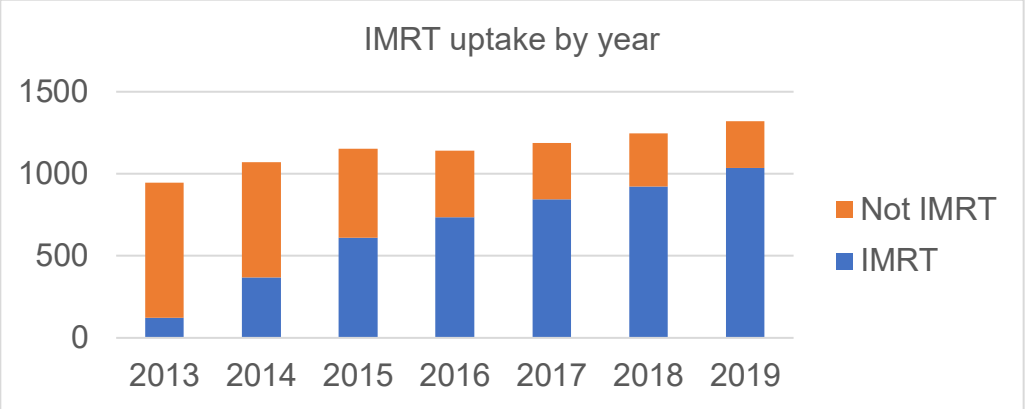
Increased uptake of IMRT improves health outcomes

The UK adoption of IMRT is evidenced by a publication of a Royal College of Radiologists audit led by Sebag-Montefiore and colleagues [**A**]. Performed between February and July 2015, 242 cases from 40/56 UK radiotherapy centres were analysed. This is the largest published prospective multicentre experience of IMRT in routine clinical practice. The UK IMRT protocol was used in 65% of cases, the remainder using the ACT2 protocol or a modified IMRT approach. Using IMRT the planned radiotherapy dose was delivered in 96% cases and radiotherapy interrupted in only 4% of cases, representing a substantial improvement compared with the ACT2 trial outcomes.

Overall, 41% of IMRT-treated patients experienced severe grade 3/4 toxicity. One-year survival was 94%. One-year patient reported outcome assessments of the IMRT treated patients found significant improvements in buttock pain, blood and mucous in stools, pain, constipation, appetite loss, and health anxiety compared to baseline. There was no evidence of clinically significant deteriorations at one year for diarrhoea, bowel frequency, and flatulence [**B**,**C**].

IMRT has dramatically impacted on the lives of anal cancer patients internationally, resulting in substantial reductions in the acute toxicity of treatment and the avoidance of interruptions in radiotherapy treatment delivery that are associated with worse survival outcomes [**D**,**E**,**F**].

Further evidence of implementation of IMRT in routine clinical practice in the English NHS is provided by the National Cancer Registration and Analysis Service, Public Health England. Prior to publication of the protocol IMRT was used in 13% of all anal cancer patients. This increased steadily to reach 78% by 2019 [**G**].



Inclusion of IMRT in national and international guidelines

The national and international reach of the shrinking field technique and IMRT is evidenced through direct reference in national and international guideline documents.

The Association of Coloproctology Great Britain and Ireland (ACPGBI) guidelines [**H**] for the management of cancer of the colon, rectum and anus state:

"Definitive CRT is the standard treatment for all anal cancers that are not amenable to local excision…and the minimum radiation dose for microscopic disease should be 40 Gy in 28 fractions over 5.5 weeks using IMRT or 30.6 Gy in 17 fractions over 3.5 weeks using the original ACT2 protocol."

They further state: "IMRT should be considered for all patients in whom definitive CRT is intended, in order to reduce acute toxicity and possibly late toxicity. Standardization of radiotherapy volume outlining, planning and delivery should be based on published consensus guidelines…A UK consensus document for outlining, planning, dose objectives and constraints and dose delivery is available on-line at http://www.analimrtguidance.co.uk/. This consensus has taken into account the excellent results achieved in the ACT2 trial, together with a review of radiotherapy planning and dose delivered to patients in the trial and has resulted in an adaptation of the recommended dose prescription."

The European Guidelines of the Medical Oncology, Surgical and Radiotherapy Organisations (ESMO-ESSO-ESTRO) guidelines [**I**] cite the ACT2 dose and radiotherapy technique and provide it as an example regimen of curative CRT for anal cancer. The United States National Comprehensive Cancer Network (NCCN) guidelines for anal carcinoma [**J**] cite the ACT2 trial outcomes, noting that "the absence of a planned treatment break in the ACT2 trial was considered to be at least partially responsible for the high colostomy-free survival rates observed in that study (74% at 3 years)."

The IMRT solution has been integrated into the CRUK-funded UK PLATO platform trial protocol, which aims to optimise radiotherapy dose for anal cancer patients with low-, intermediate- and high-risk disease. Sebag-Montefiore is Chief Investigator and has recruited over 400 patients to date in this uncommon disease. The trial platform includes three anal cancer trials (ACT) 3,4 and 5. The above IMRT technique is used to allow the ACT4 trial to test the benefit of de-escalation of radiotherapy dose in early stage disease and ACT5 trial to test the benefit of dose escalation in locally advanced disease.

5. Sources to corroborate the impact (indicative maximum of 10 references)

A. R, Drinkwater K, O'Cathail SM, Adams R, Glynne-Jones R, Harrison M, Hawkins MA, **Sebag-Montefiore D**, Gilbert DC. Initial results from the Royal College of Radiologists' UK National Audit of Anal Cancer Radiotherapy 2015. *Clin Oncol (R Coll Radiol)*. 2017;29(3):188-197. DOI: 10.1016/j.clon.2016.10.005

B. Jones CM, Adams R, Downing A, Glynne-Jones R, Harrison M, Hawkins M, **Sebag-Montefiore D**, Gilbert DC, Muirhead R. Toxicity, tolerability, and compliance of concurrent Capecitabine or 5-Fluorouracil in radical management of anal cancer with single-dose Mitomycin-C and intensity modulated radiation therapy: Evaluation of a national cohort. *Int J Radiat Oncol Biol Phys*. 2018;101(5):1202-121. DOI: 10.1016/j.ijrobp.2018.04.033

C. Gilbert A, Drinkwater K, McParland L, Adams R, Glynne-Jones R, Harrison M, Hawkins M, **Sebag-Montefiore D**, Gilbert DG, Muirhead R. UK national cohort of anal cancer treated with intensity-modulated radiotherapy: One-year oncological and patient-reported outcomes. *Eur J Cancer* 2020;128:7-16. DOI: 10.1016/j.ejca.2019.12.022

D. Letter from the Deputy Chair of the National Cancer Research Institute Clinical and Translational Radiotherapy Research Working Group

E. Letter from the Medical Director, Professional Practice, Clinical Oncology, Royal College of Radiologists UK

F. Letter from NIHR National Specialty Lead Radiotherapy and Imaging

G. Data provided by the Radiotherapy Dataset (RTDS) Project Lead for National Cancer

Registration & Analysis Service, Public Health England from Cancerstats2

H. Geh I, Gollins S, Renehan A, Scholefield J, Goh V, Prezzi D, Moran B, Bower M, Alfa-Wali M, Adams R. Association of Coloproctology of Great Britain & Ireland (ACPGBI): Guidelines for the management of cancer of the colon, rectum and anus (2017) - Anal Cancer. *Colorectal Dis*. 2017;19 Suppl 1:82-97. DOI: 10.1111/codi.13709

I. Glynne-Jones R, Nilsson PJ, Aschele C, Goh V, Peiffert D, Cervantes A, Arnold D. Anal cancer: ESMO-ESSO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2014;25(Suppl 3): iii10–iii20. DOI: 10.1093/annonc/mdu159

J. Benson AB, Venook AP, Al-Hawary MM, Cederquist L, Chen YJ, Ciombor KK, Cohen S, Cooper HS, Deming D, Engstrom PF, Grem JL, Grothey A, Hochster HS, Hoffe S, Hunt S, Kamel A, Kirilcuk N, Krishnamurthi S, Messersmith WA, Meyerhardt J, Mulcahy MF, Murphy JD, Nurkin S, Saltz L, Sharma S, Shibata D, Skibber JM, Sofocleous CT, Stoffel EM, Stotsky-Himelfarb E, Willett CG, Wuthrick E, Gregory KM, Freedman-Cass DA. Anal Carcinoma, Version 2.2018, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2018 Jul;16(7):852-871. DOI: 10.6004/jnccn.2018.0060