Institution: University of Birmingham

Unit of Assessment: A1

Title of case study: The introduction of combination chemo-radiotherapy to reduce the need for cystectomy in patients with muscle invasive bladder cancer

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

Muscle invasive bladder cancer is the sixth most common cancer and remains a major cause of death and suffering worldwide. The standard treatment for advanced bladder cancer has been surgical removal of the bladder (cystectomy) which is associated with considerable morbidity. Many (20%) patients are elderly, with significant co-morbidities and hence are high risk for a major operation. In the past patients who were not able to undergo surgery were offered palliative radiotherapy. Research at the University of Birmingham has shown that the addition of low toxicity chemotherapy to radiotherapy is as effective as cystectomy in controlling disease progression and has minimal impact on bladder function. This new approach is an excellent alternative to cystectomy and has been adopted as a new standard of care thus demonstrating considerable impact on clinical practice and patient outcome.

2. Underpinning research (indicative maximum 500 words)

Bladder cancer is one of the most common cancers in the world with an estimated 382,000 cases annually. Early stage disease is treated with local resection but muscle invasive disease carries a poor prognosis and has generally been managed by surgical removal of the bladder with introduction of the ureters into the bowel (cystectomy). This procedure carries substantial morbidity and is also unsuitable for elderly patients, who are then generally offered palliative radiotherapy. The aim of the research described here was to provide evidence for a new approach combining radiotherapy with chemotherapy as an alternative approach to cystectomy.

In 1996 a small randomised study demonstrated the efficacy of cisplatinum in bladder cancer, but the drug is potentially toxic and patients must have good kidney function before being considered for treatment. UK experience showed that this approach was not suitable for at least 50% of patients due to toxicity and the poor general condition of patients. As a result, the University of Birmingham team undertook a phase I and phase II study which ran from 1997 to 2000 (Principal Investigator Prof Nicholas James, at UoB since 1994) using a regimen of mitomycin C and 5-fluorouracil which was predicted to be better tolerated. These preliminary studies determined the doses of chemotherapy and radiotherapy that could be delivered safely to patients of 70+ years (1-5).

In 2001 Professor James obtained funding from the Cancer Research Campaign to commence a large confirmatory phase III trial called BC2001 which compared radiotherapy alone with chemo-radiotherapy for the treatment of muscle invasive bladder cancer. The study compared different radiotherapy techniques and collected detailed data on the effect of radiotherapy planning techniques on toxicity outcomes. An important observation was that the addition of chemotherapy did not impact on the delivery rate of the radiotherapy.

When recruitment closed in 2010, 458 patients had been entered into study making this the largest ever trial of radiotherapy in bladder cancer. The analysis showed that radical radiotherapy combined with low dose chemotherapy was very well tolerated, even by elderly patients. Indeed the median age of the group was 72 years and 15% were aged 80 years or more. Moreover the treatment was highly effective and led to a 43% reduction in the rate of pelvic relapse (6).

A general perception amongst many urologists around the world has been that radiotherapy leads inevitably to damage to the bladder such that organ becomes shrunken and poorly functioning following treatment. It therefore became important for the University of Birmingham team to demonstrate that the function of the bladder was retained following radiotherapy and that the

addition of chemotherapy did not further adversely affect organ function. Remarkably, bladder function following radiotherapy and chemotherapy was excellent. Short-term side effects during treatment were mild to moderate and over 70% of patients reporting no long-term side effects at all (6).

Overall these results demonstrate that chemo-radiotherapy is an excellent treatment option for patients with muscle invasive bladder cancer. Importantly this is particularly true for the frail or the elderly, and thus considerably extends the population to which potentially curative treatment can be administered.

The primary research output of the trial was disseminated through several major meetings in 2010 including plenary sessions at the American Society of Radiation Oncology (ASTRO) and the National Cancer Research Institute (NCRI) Annual Meeting. Following the ASTRO presentation Professor James received invitations from the Editors of both the *New England Journal of Medicine (NEJM)* and *Journal of the American Medical Association* to submit the full analysis. The paper was published in the *NEJM* in 2012 (6) and was accompanied by an editorial that described the trial as 'indeed remarkable' and a 'landmark study' which 'is potentially practice changing for patients with muscle-invasive bladder cancer'. The paper was also featured on the US National Cancer Institute website.

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

1. Hussain SA, Moffitt DD, Glaholm J, et al: A Phase I/II Study Of Synchronous Chemoradiotherapy For Poor Prognosis Locally Advanced Bladder Cancer. Annals of Oncology 12:929-935, 2001 *PMID:11521797*
2. Hussain SA, James ND: Organ preservation strategies in bladder cancer. [Review] [89 refs]. Expert Review of Anticancer Therapy 2:641-651, 2002 *doi:10.1586/14737140.2.6.641*
3. Hussain SA, James ND: The systemic treatment of advanced and metastatic bladder cancer. Lancet Oncol 4:489-497, 2003 *doi:10.1016/S1470-2045(03)01168-9*
4. Hussain SA, Stocken DD, Peake DR, et al: Long-term results of a phase II study of synchronous chemoradiotherapy in advanced muscle invasive bladder cancer. Br.J Cancer 90:2106-2111, 2004 *doi:10.1038/sj.bjc.6601852*
5. James N, Hussain SA: Management of muscle invasive bladder cancer--British approaches to organ conservation. Semin.Radiat Oncol 15:19-27, 2005 *PMID: 15662603*
6. James ND, Hussain SA, Hall E, et al: Radiotherapy with or without chemotherapy in muscle-invasive bladder cancer. The New England Journal of Medicine 366:1477-88, 2012) *DOI: 10.1056/NEJMoa1106106*

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

The research conducted by Prof Nick James has had a significant impact on **clinical practice** and **patients** with muscle invasive bladder cancer.

Impact on patients

The demonstration by the BC2001 trial that combination chemotherapy and radiotherapy can offer the potential of disease cure whilst preserving conservation of bladder function means that it can now be offered as a definitive treatment option compared to the previous standard of chemotherapy followed by cystectomy. Cystectomy is a major operation and is associated with considerable morbidity and mortality, and permanent loss of urinary function. Patients can now make a choice in their treatment to choose a non-surgical option. The new options available for patients with bladder cancer were detailed in an editorial in the New England Journal of Medicine 2012 (1), which stated that '***The development of organ-sparing procedures in breast and prostate cancer was promoted by vocal patient advocacy groups with the use of the Internet and social networking. We anticipate that the publication of this important study will help patients with bladder cancer to find their voice***'.

In addition, cystectomy is unsuitable for many elderly patients and as such these patients were

previously considered suitable only for palliative radiotherapy which offered no prospect of cure. This was articulated in the NEJM editorial by Shipley (1), who commented that '***35% of patients between the ages of 70 and 80 years received no potentially curative therapy at all, a proportion that increased to 55% among patients 80 years of age or older'***. As the number of elderly people increases, the importance of this less invasive and potentially curative therapy becomes even more significant.

Impact on practice

There is already clinical evidence that the BC2001 trial has changed clinical practice in the UK. The number of cystectomies for bladder cancer had shown a relentless increase over the last few years and peaked at 150 per month in October 2012. Since that time the rate has fallen by 23% to 115 in May 2013, the latest time for which results are available (2). The change in clinical practice described and associated reduction in the number of cystectomies has and will continue to deliver economic impact to healthcare providers, as the cost of treatment and the number of in patient days will be reduced.

The change in clinical practice has been confirmed by the Chair of the National Cancer Research Institute Bladder Clinical Studies Group, who detailed in a statement that "***it is confirmed that the chemotherapy plus radiotherapy regime is now acknowledged as the gold standard non-surgical treatment schedule for muscle invasive bladder cancer and is now the standard arm for any future studies in this area***" (3). The outcomes from the research have also changed clinical practice internationally, with the use of the combined chemo-radiotherapy being used as the new 'standard of care' and the incorporation of the bladder sparing regime as a standard arm in US trials, this is strong evidence of a change in clinical practice and can be evidenced by the trial being run by the Radiation Therapy Oncology Group at the US National Cancer Institute (4).

The change in clinical practice is further evidenced by the National Cancer Research Institute Bladder Clinical Studies Group Annual Report 2013 (5), which states: "***The BC2001 trial of chemoradiation versus radiation alone (Chief Investigator: Professor Nick James) has changed standard of care for patients with T2-T4 bladder cancer in the UK and internationally. The study is the largest ever chemoradiation or chemotherapy study in bladder cancer, showing improvements in local control equivalent to those seen in cervical cancer chemoradiation. Many centres both in the UK and internationally have adopted its treatment schedule as standard practice***".

The change in clinical practice is now reflected in published guidelines, e.g. the Pan Birmingham Cancer Network Guideline (6). Point 8.5 details: "***Based on the results of the BC2001 trial patients receiving radical radiotherapy should be offered synchronous chemotherapy with continuous infusion 5FU plus a single bolus of mitomycin C on day 1. The trial showed a 50% reduction in invasive recurrence with no increase in late toxicity or impact on bladder capacity at 1 year. The synchronous regimen toxicity was not adversely impacted by prior neoadjuvant chemotherapy***".

Impact on Surgical Education

Professor James has been an invited speaker at Educational sessions for practitioners at nine International conferences to date and contributed a chapter to the President of American Society of Clinical Oncology's '*Building Bridges in Oncology*' supplement for 30,000 oncologists at the American of Clinical Oncology meeting in 2013 (7). James has been invited to author the chapter on Bladder Cancer for the highly influential US text Perez & Brady's '*Principles and Practice of Radiation Oncology'* (8), one of a very small number of non-US authors and as clinical trainees use this textbook worldwide this will lead to the work being embedded in practice globally.

This work in bladder preservation has taken a long time to recruit and mature. This has been driven by a strong sense in the surgical community that cystectomy should be offered to as many patients as possible, with radiotherapy reserved for palliation or the very elderly on unfit. To recruit large numbers of patients to a randomised trial thus required substantial efforts to convince clinicians of the importance of improving non-surgical therapies. To achieve this, investigators'

meetings and workshops were held to emphasise the importance of studying alternatives to surgery. This was backed up by writing review articles in major journals and speaking at meetings on the topic. As the trial progressed, the recruitment rate improved as clinicians had more confidence in the safety and efficacy of the schedules being tested, hence just running the trial prepared the ground for a change in practice.

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

1. Shipley W, Zietman A. Old drugs, new purpose--bladder cancer turning a corner. New England Journal of Medicine. 2012; **366**. Editorial written by two Professors of Radiation Oncology (Prof Anthony Zietman or Prof William Shipley) from Harvard describing the trial as a "landmark study" and "practice changing".
2. NHS Hospital Episode Statistics data report
3. Letter from the Chair of the National Cancer Research Institute Bladder Clinical Studies Group.
4. http://www.cancer.gov/clinicaltrials/search/view?cdrid=654727&version=Patient&protocolsearchid=6312750
5. National Institute for Health Research/National Cancer Research Institute/National Cancer Research Network – Bladder Cancer Clinical Studies Group Annual Report 2012/2013 (page 8)
6. Pan Birmingham Cancer Network Guideline
7. ASCO supplement - Building Bridges to Conquer Cancer, ASCO Educational Supplement 2013
8. Website of Perez & Brady's 'Principles and Practice of Radiation Oncology'. http://www.amazon.co.uk/Bradys-Principles-Practice-Radiation-Oncology/dp/078176369X