

Original Article

# Anaemia is Associated with Poor Overall Survival but not with Inferior Local Control in Patients with Muscle Invasive Bladder Carcinoma Treated by Radical External Beam Radiotherapy. A Retrospective Study

C. P. Joynson\*, S. Sundar†, P. Symonds\*

\*Department of Oncology, Leicester Royal Infirmary, Leicester, UK; †Department of Oncology, Nottingham City Hospital, Nottingham, UK

## ABSTRACT:

**Aims:** The treatment of muscle invasive transitional cell carcinoma of the bladder with radiotherapy allows organ preservation and is frequently used in the UK, especially in patients not medically fit for cystectomy. Anaemia is known to be an indicator of a poor response to radiotherapy in head and neck and cervical carcinomas. Here we describe the prevalence and type of anaemia in patients with transitional cell carcinoma of the bladder and determine the effect anaemia has on treatment outcome.

**Materials and methods:** A retrospective review of notes was carried out on patients treated radically between 1992 and 1997. Potential patient, tumour and treatment prognostic indicators were reported. Patients were labelled as being anaemic if their pre-treatment haemoglobin level was below the normal range (below 13.5 g/dl for men and below 11.5 g/dl for women). The time to local failure, metastases and overall survival were recorded. Recurrence-free survival and overall survival actuarial estimations were carried out using the Kaplan–Meier method and compared by Log-rank testing. A multivariate analysis was carried out using the Cox regression method.

**Results:** Data on 100 patients were available for analysis. Most of the patients were not adequately staged by today's standards. Fifty-two patients were anaemic, with 75% of them having a normochromic, normocytic anaemia. The univariate analysis showed no significant difference in the time to local recurrence, a trend towards a shorter time to metastases and a significant reduction in overall survival in anaemic patients ( $P = 0.001$ ). Two-year survival was 43% and 22% for non-anaemic and anaemic patients, respectively. A multivariate analysis using the covariates tumour stage, grade and serum creatinine found anaemia to be a poor prognostic indicator for overall survival ( $P = 0.005$ ).

**Conclusion:** Anaemia is highly prevalent in patients with bladder cancer. This retrospective study showed anaemic patients to have a worse outcome with radiotherapy treatment than patients with a normal haemoglobin level. This was not accounted for by a difference in local control, which may be expected from hypoxic radiobiological principles. Anaemia may be indicative of more aggressive malignancy or subclinical metastases. Joynson, C. P. *et al.* (2006). *Clinical Oncology* 18, 728–734

© 2006 The Royal College of Radiologists. Published by Elsevier Ltd. All rights reserved.

**Key words:** Anaemia, bladder cancer, erythrocyte indices, radioresistance, radiotherapy, tumour hypoxia

## Introduction

Bladder carcinoma remains a major health problem, with an estimated incidence of 19 per 100 000 population in the western world. Worldwide, in 2002, there were more than 350 000 new cases of bladder cancer and 145 000 cancer deaths from the disease [1].

The management of invasive bladder carcinoma remains controversial. The standard of care in the USA and many other countries is radical cystectomy. Radiotherapy with salvage cystectomy is offered as an equally effective option in the UK and some other countries. There have been no

prospective, randomly controlled clinical trials directly comparing the two treatments. A Cochrane meta-analysis concluded that surgery was the most effective treatment option, but only three small trials were included, all of which took place before recent advances in surgery and radiotherapy [2].

Radical radiation therapy can achieve bladder preservation and is often the treatment of choice for patients, particularly older patients, who may not be surgical candidates on the grounds of comorbidity or patient choice. However, the results from radiotherapy have remained disappointing, probably because of selection bias, with

modern series reporting a 5-year overall survival of 31.7–37.2% [3].

Various strategies are being trialled to improve the outcome of primary radical radiotherapy. Conformal radiotherapy improves target coverage and reduces toxicity and is now well established. Chemotherapy is currently being assessed in early bladder cancer. A small Canadian trial has shown improved local control with concurrent cisplatin chemotherapy and radiotherapy [4]. Concurrent chemoradiation is currently being tested in large phase III trials. The results from two meta-analyses showed at least a 5% absolute benefit in 5-year survival with neoadjuvant cisplatin-based chemotherapy [5,6]. Reducing geographical miss, dose escalation, acceleration of treatment regimens and the use of intensity-modulated radiotherapy are all potential mechanisms for improving future results from bladder radiotherapy [7].

In locally advanced solid tumours, tumour hypoxia is an important factor in the radioresistance of the tumour. Irradiation causes cell death when ionising radiation forms free radicals from molecular oxygen that introduces breaks into tumoral DNA.

Low concentrations of oxygen prevent the formation of free radicals and enhance radioresistance. Intratumoral hypoxia results from an imbalance between the supply and consumption of oxygen. The pathogenic mechanisms include structural and functional abnormalities of the tumour microvasculature, increased diffusion distances and anaemia. Anaemia is a contributory factor to hypoxia as reduced haemoglobin levels lower the partial pressure of oxygen in the blood, resulting in a reduced oxygen supply to already hypoxic tumours [8]. Hypoxia manipulation is an attractive strategy to improve the outcome of bladder radiotherapy. Studies with hypoxia-modifying treatments have shown mixed results. A Medical Research Council-sponsored trial (BCON) is currently evaluating the role of oral nicotinamide and carbogen gas given concurrently with radiotherapy.

In head and neck and cervical cancers there is now good evidence to suggest that haemoglobin levels can be predictive of tumour control [9–12]. Patients with bladder cancer frequently present with haematuria and anaemia is a common finding in these patients. Six studies have investigated haemoglobin levels in bladder cancer treated with radiotherapy with conflicting results [13–18].

Both Quilty and Duncan [13] and Gospodarowicz *et al.* [14] reported a pre-treatment haemoglobin concentration below 12 g/dl to be a poor prognostic indicator for tumour response, local control and overall survival.

To the authors' knowledge, previous studies have not looked at the type of anaemia seen in bladder cancer. The anaemia could be an iron-deficient, microcytic anaemia due to a loss of blood through haematuria, or it could be a cancer-related anaemia, which is typically a normocytic, normochromic anaemia.

In this study, we retrospectively analysed data from patients treated with radical radiotherapy for muscle invasive transitional cell carcinoma. We hypothesised that anaemia would be prognostic for poor local control with

radiotherapy and that an iron-deficient type microcytic anaemia would be the most common subtype.

## Materials and Methods

Leicester Royal Infirmary is a specialist cancer centre serving a population of 1 000 000. We undertook a retrospective review of patients with transitional cell carcinoma treated with radical radiotherapy between January 1992 and December 1997. Patients were identified from the hospital database. Patient characteristics (age, gender, pre-treatment creatinine), tumour characteristics (grade, stage, presence of ureteric obstruction and carcinoma *in situ* [CIS]), treatment characteristics (radiation dose and schedule) and haematological characteristics (pre-treatment haemoglobin, mean corpuscular volume, mean corpuscular haemoglobin) were collected from patient notes and the hospital haematological computer base.

The response at the first check cystoscopy, the time to local disease progression, the time to metastatic disease and overall survival were recorded for all patients.

### Definition of Anaemia

Patients were classified as anaemic if they had a pre-treatment haemoglobin level below the hospital's normal range. The normal range for haemoglobin was 13.5–18 g/dl for men and 11.5–16.5 g/dl for women. A patient's blood film was described as microcytic, normocytic or macrocytic, depending on the erythrocyte mean corpuscular volume and microchromic, normochromic or macrochromic depending on the erythrocyte mean corpuscular haemoglobin.

### Radiation Technique

All patients were treated by the department protocol at the time. Patients were computed tomography planned in a supine position with an empty bladder. During the time period of the study, two different treatment plans were used. Earlier patients were treated in two phases with the whole pelvis being treated with anterior and posterior fields in the first phase and a second phase boost using three fields to the bladder plus a margin of 2 cm. Later patients were treated in a single phase with three fields treating the planning target volume, which consisted of the bladder plus a margin of 2 cm isometrically. The technique was individualised for each patient. An isocentric technique was used for the three-field plan and the dose prescribed to the 100% isodose. Patients were treated with 6–8 MV photons. The doses to the prescription point were either 60–64 Gy in 2 Gy fractions or 50–55 Gy in 2.75 Gy fractions.

### Treatment Outcomes

Patients were followed up by both an oncologist and a urologist. Local disease relapse was defined as histologically confirmed disease at cystoscopy, and therefore

Download English Version:

<https://daneshyari.com/en/article/5700155>

Download Persian Version:

<https://daneshyari.com/article/5700155>

[Daneshyari.com](https://daneshyari.com)