Clinical Oncology 27 (2015) 519–526

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Original Article

The Importance of Prostate-specific Antigen (PSA) Nadir and Early Identification of PSA Relapse after 10 Years of Prostate Iodine^{125} Seed Brachytherapy in Edinburgh

D.B. McLaren *, G. Kerr *, A.B. Law *, J.P. Brush †, J. Keanie †, J. Malik *, W. Keough *, T. Ronaldson *, J. Lee *, T. Kehoe *

* *Edinburgh Cancer Centre, Edinburgh, UK*
† *Western General Hospital, Edinburgh, UK*

Received 28 November 2014; received in revised form 10 April 2015; accepted 12 May 2015

Abstract

Aims: To analyse our 5 and 10 year prostate brachytherapy outcome data and to assess the impact of PSA nadir on relapse free survival and whether an alternative definition of PSA relapse could detect men destined to fail by the Phoenix definition at an earlier time point.
Materials and methods: 474 men were treated over a 10 year period between 20012 and 2011and divided into 2 five year cohorts for the purpose of the analysis.
Results: The risk of relapse is strongly predicted by post treat prostate-specific antigen (PSA) nadir. After 3 years post-treatment, PSA nadir plus 0.4 ng/ml identified men at risk of relapse 17 months earlier than the Phoenix definition.
Conclusion: The Phoenix definition of nadir plus 2.0 ng/ml does not allow the early identification of men destined to relapse. The initiation of salavage therapy at the earliest opportunity could potentially affect subsequent survival and an outline randomised controlled trial proposal is presented.

Key words: Iodine^{125} seed brachytherapy; prostate cancer; PSA nadir; relapse; salvage treatment

Introduction

In August 2001, Edinburgh treated the first patient in Scotland with iodine^{125} low dose rate seed brachytherapy for early stage prostate cancer. This is the first Scottish data to be presented and we present the results for patients treated during the first 10 years. These data reflect a non-screened population and include patients with intermediate and high risk features. Durable long-term outcome data are now available; however, late local relapse can still occur in all series reported [1]. The early identification of patients at risk of local relapse would allow potentially curative salvage therapy to be initiated at the earliest opportunity. The identification of true prostate-specific antigen (PSA) failure versus a PSA bounce can be difficult and it requires a period of ongoing assessment, usually beyond year 3 from treatment. Here we present data to identify those men at greatest risk of local failure by the Phoenix definition and whether it is possible to identify future relapse at an earlier time point based on PSA nadir plus 0.4 ng/ml.

Materials and Methods

Between August 2001 and August 2011, 474 patients received treatment for early stage (T1/2N0M0), histologically confirmed prostate cancer using iodine^{125} seed brachytherapy. Patient characteristics are shown in Table 1. Our early technique was based on the Seattle technique with an initial volume study, pre-plan and subsequent implant under a general anaesthetic 2 weeks later [2]. In 2008 we moved to a single dynamic intraoperative implant technique under a single general anaesthetic. Seed activity increased from 0.323 mCi (0.41 U) to 0.387 mCi (0.491 U) at

Author for correspondence: D.B. McLaren, Edinburgh Cancer Centre, Western General Hospital, Crewe Road, Edinburgh EH4 2XU, UK. Tel: +44-131-537-2215; Fax: +44-131-537-1029.
E-mail address: duncan.mclaren@luht.scot.nhs.uk (D.B. McLaren).

http://dx.doi.org/10.1016/j.clon.2015.05.003

Table 1
Patient characteristics and D90 in each cohort

	2001–2006	2006–2011	Total
Number	216	258	474
Age			
Median	63	63	63
Range	45–76	44–78	44–78
Initial prostate-specific antigen			
Median	7.8	6.9	7.2
Range	0.9–34.4	1.5–24.8	0.9–34
T stage			
1	135 (62.5)	153 (59.3)	288 (60.8)
2	81 (37.5)	105 (40.7)	186 (39.2)
Gleason score			
5	4 (1.9)	2 (0.8)	6 (1.7)
6	152 (70.4)	151 (58.5)	303 (63.9)
7	56 (25.9)	102 (39.5)	158 (33.3)
8	4 (1.9)	3 (1.2)	7 (1.5)
Prognostic group			
Good	117 (54.2)	119 (46.1)	236 (49.8)
Intermediate	80 (37.0)	117 (45.3)	197 (41.6)
Poor	19 (8.8)	22 (8.5)	41 (8.6)
Neoadjuvant hormones			
Yes	69 (31.9)	37 (14.3)	106 (22.4)
No	147 (68.1)	221 (85.7)	368 (77.6)
Prostate volume			
Median	35	35	35
Range	16–57	13–57	13–57
D90 dose (Gy)			
Median	136.1	148.1	143.5
Range	51.4–220.2	80.0–201.1	51.4–220.2
Patient numbers D90			
< 125	61 (28.2%)	37 (14.3%)	98 (20.7%)
155+	40 (18.5%)	93 (36.0%)	133 (28.1%)
Not carried out	23 (10.6%)	22 (8.5%)	45 (9.5%)

Table 2
Proportional hazards analysis of prostate-specific antigen (PSA) relapse

	P value
474 patients, 69 relapses	
Cohort	ns
Age	ns
Prognostic group	<0.0001 (chi square = 26)
Volume	ns
Neoadjuvant hormones	ns
429 patients, 61 relapses where additional D90 information available	
Cohort	ns
Age	ns
Prognostic group	<0.0001 (chi square = 21)
Volume	ns
Neoadjuvant hormones	ns
D90	0.0022
474 patients, 69 relapses breaking prognostic group into constituent parts	
Cohort	ns
Age	ns
T	ns
Gleason score	ns
PSA at presentation	<0.0001 (chi square = 33)
Neoadjuvant hormones	ns
429 patients, 61 relapses where additional D90 information available	
Cohort	ns
Age	ns
T	ns
Gleason score	ns
PSA at presentation	<0.0001 (chi square = 41)
Volume	0.0068
Neoadjuvant hormones	ns
D90	ns

this time, but dose-volume histogram constraints remained unchanged, as did the prescription dose of 145 Gy. Post-implant computed tomography-based dosimetry was carried out at day 28 in 429 (90.5%) patients.

Follow-up with serial PSA measurements was 3 monthly in the first year and 6 monthly thereafter. If the PSA level continued to fall after 3 years then follow-up continued at 6 monthly intervals with the patient visiting their general practitioner for a PSA check and completing a postal questionnaire for return to the department. The patients included in this study were identified from the departmental database and relevant data were extracted from the database and from review of the case notes as required.

The Kaplan–Meier method was used to calculate actuarial estimates of survival rates and PSA relapse rates. PSA relapse was defined as a rise of >2.0 ng/ml above the nadir, as per the Phoenix definition [3]. Multivariate analysis to identify independent prognostic factors was carried out using the Cox proportional hazards method (Tables 2, 3). The data were split into two 5 year cohorts (cohort 1 2001–2006 and cohort 2 2006–2011) in order to check for any change in selection for treatment over the period of the review and to access the effect of a learning curve. Patients were divided into poor, intermediate and good prognostic groups using the method of Zelefsky *et al.* [4]. Both the prognostic groups and the constituent parts (T stage, Gleason score and PSA at presentation) were used separately in the multivariate analyses (Table 4). Patients were identified as having a PSA bounce if their post-treatment PSA rose by more than 0.2 ng/ml after an initial response to treatment and then fell again.

Results

Survival

The median follow-up was 6.5 years. Only 40 patients have died. The overall survival rate at 5 years was 96.3% (94.5% in the first cohort and 98.2% in the second) and 85.3% at 10 years (95% confidence interval 79.7–90.4%). Only 15 patients have died with active prostate cancer present, all in the first cohort. Eleven had metastatic disease and one died of carcinoma colon with a PSA that had climbed to 10.3 ng/