DR. ROBERT JOHN RULACH (Orcid ID : 0000-0002-3148-0647)

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Real World Uptake, Safety Profile and Outcomes of Docetaxel in Newly Diagnosed Metastatic Prostate Cancer

Robert Rulach[a] MRCP, Stephen McKay[a] FRCR, Sam Neilson[a] MBChB, Lillian White[b] MSc, Jan Wallace[a] FRCR, Ross Carruthers[a] FRCR, PhD, Carolynn Lamb[a] FRCR, Almudena Cascales[a] MD, MSc, Husam Marashi[a] FRCR, Hilary Glen[a] PhD, Balaji Venugopal[a,c] FRCP, MD, Azmat Sadoyze[a] FRCR, Norma Sidek[a] FRCR, J. Martin Russell[a,c] FRCR, Abdulla Alhasso[a] FRCR, David Dodds[a] FRCR, Jennifer Laskey[a] MSc, Robert J. Jones[a,c*] FRCP, PhD, and Nicholas MacLeod[a*] FRCR, MD

[a]The Beatson West of Scotland Cancer Centre, 1053 Great Western Road, Glasgow, G12 0YN, UK

[b]University Hospital Ayr, Dalmellington Road, Ayr, KA6 6DX, UK

[c]The University of Glasgow, University Avenue, Glasgow, G12 8QQ, UK

* Both Prof Jones and Dr MacLeod are joint lead authors

Corresponding Author

Dr Robert Rulach

Level 4 Offices

The Beatson West of Scotland Cancer Centre

1053 Great Western Road, Glasgow, G12 0YN, UK

Telephone number: +44 141 301 7000

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Fax number: +44 141 301 7124
E-mail: robert.rulach@nhs.net

Abstract

Objectives: To investigate the uptake, safety and efficacy of docetaxel chemotherapy in hormone-naïve metastatic prostate cancer (mPC) in the first year of use outside of a clinical trial.

Subjects/patients and Methods: Patients in the West of Scotland Cancer Network (WoSCAN) with newly diagnosed mPC were identified from the regional multidisciplinary team (MDT) meetings and their treatment details were collected from electronic patient records. The rate of febrile neutropenia, hospitalisations, time to progression and overall survival were compared between those patients who received docetaxel and androgen deprivation therapy (ADT), or ADT alone using survival analysis.

Results: Out of 270 eligible patients, 103 received docetaxel (38.1%). 35 patients (34%) were hospitalised and there were 17 episodes of febrile neutropenia (16.5%). Two patients (1.9%) died within 30 days of chemotherapy. Patients who received ADT alone had an increased risk of progression (HR 2.03, 95% CI (1.27, 3.25), log-rank test, p= 0.002) and had an increased risk of death (HR 5.88, 95% CI 2.52, 13.72, log-rank p=0.001) compared to the docetaxel group. The risk of febrile neutropenia was nine times greater if chemotherapy was started within three weeks of ADT initiation (95% CI (1.22,77.72) p= 0.032).

Conclusion: Docetaxel chemotherapy in hormone-naïve mPC has significant toxicities, but has a similar effect on time to progression and overall survival as seen in randomised trials. Chemotherapy should be started 3 weeks or more after androgen deprivation.

Keywords: Docetaxel, Hormone-naïve, Metastatic, Prostate Cancer, Real World

Introduction

Across the UK, approximately 11,300 men died from prostate cancer in 2014, making it the second most common cause of cancer death in males. The majority of these deaths are in men over the age of 80, and those diagnosed with metastatic disease have a five-year survival of only 30% [1]. Most patients with metastatic prostate cancer (mPC) respond initially to androgen suppression but invariably become resistant to hormone manipulation. For patients with hormone-resistant mPC, docetaxel has been the standard of care for over a decade, with a median improvement in overall survival of 2.9 months when compared to mitoxantrone [2],[3].

However, recent clinical trials showed a larger overall survival gain when docetaxel is given in the hormone-naïve setting. Two large randomised controlled trials, STAMPEDE [4] and CHAARTED [5], both showed a significant benefit in overall survival when docetaxel chemotherapy was added to standard androgen deprivation therapy (ADT) near the time of initiation. The median survival gain reported in these studies was 10 and 13.6 months respectively, and in a subgroup analysis of the STAMPEDE data, the effect was larger in patients with metastatic (M1) disease. Although an earlier French study, GETUG-AFU 15 [6],

did not show a significant benefit, meta-analysis of these three trials confirms a clear survival gain for patients with mPC [7]. In the STAMPEDE study, the rate of grade 3 or above adverse events in the first year was 51% in the chemotherapy and ADT arm compared to 31% in the standard of care arm. The toxicity in the chemotherapy arms became equivalent to the standard of care (SOC) arm after the first year. There were 8 chemotherapy related deaths in the docetaxel containing arms of STAMPEDE (0.67%).

The West of Scotland Cancer Network (WoSCAN) establishes protocols and pathways for the care of all National Health Service (NHS) patients within a catchment area of 2.8 million people. WoSCAN recruited actively to the STAMPEDE trial, and was able to change practice within days of the release of the STAMPEDE results. In June 2015 the WoSCAN clinical management guideline for newly-diagnosed mPC changed with the addition of docetaxel chemotherapy to ADT in hormone-naïve mPC patients fit enough to receive it.

The data presented here analyse the safety and efficacy of docetaxel chemotherapy in hormone-naïve prostate cancer in the first year of use outside of a clinical trial.

Subjects/patients and methods

Patients and Data collection

All patients discussed in the four multi-disciplinary team (MDT) meetings within WoSCAN (Lanarkshire, Ayrshire and Arran, Pan-Glasgow and Forth Valley) between 6th June 2015 and 2nd June 2016, who were newly diagnosed with mPC were included in this analysis. The MDT

confirmed the diagnosis and staging of every new prostate cancer on the basis of either biopsy (of either primary or metastases) and/or PSA greater than 100ng/ml with abnormal digital rectal examination (DRE). In patients who were unfit for biopsy and had a PSA of less than 100ng/ml, the diagnosis was made clinically by the MDT. Metastatic disease was diagnosed on imaging (computed tomography (CT), magnetic resonance imaging (MRI) or isotope bone scan). Patients who had previous local treatment and developed subsequent metastases were excluded. The decision to commence docetaxel was made by the treating oncologist. Each health board approved the release of patient information for this study.

Baseline patient characteristics were collected from electronic patient records including age, Gleason score (if available), peak pre-ADT PSA, pre-ADT haemoglobin, pre-ADT alkaline phosphatase (ALP), pre-biopsy neutrophil lymphocyte ratio (NLR), pre-biopsy haemoglobin, and performance status as measured by the referrer to the MDT or the treating oncologist.

The following treatment characteristics were obtained from electronic patient records and from Chemocare (an online platform to prescribe chemotherapy): type of ADT, date ADT commenced, date of starting chemotherapy, number of cycles of chemotherapy, hospital admissions within 30 days of chemotherapy, dose reductions, delayed treatments, time to PSA nadir, time to biochemical progression, neutropenic events and date of death. Time to PSA nadir and to biochemical progression were measured from the date of commencing ADT. Biochemical progression was deemed to have occurred if the PSA value had increased by 50% above nadir value, or, if the nadir value was less than 4ng/ml, the greater of either a 50% rise from nadir or a PSA above 4ng/ml. Primary treatment failure was defined as a nadir

of greater than 50% of the initial PSA. Overall survival was measured from date of diagnosis to date of death, and the cut-off for data-analysis was 10th February 2017.

The chemotherapy protocol consisted of docetaxel 75mg/m^2 given on day 1 every 3 weeks plus prednisolone 5mg twice daily for a total of 6 cycles. Granulocyte-colony stimulating factors (G-CSF) were not routinely prescribed. Dose reductions and delays were at the treating oncologist's discretion. The choice of ADT was as per regional protocols.

Statistical analysis

Baseline characteristics were compared using either Chi-squared or the Student's t-test. Time to progression and overall survival was calculated using Kaplan-Meier plots and the log-rank test. Hazard ratios were obtained using Cox regression. Logistic regression was used to derive odds ratios for the risk of febrile neutropenia against time. All statistical analyses were performed using SPSS (Version 23, IBM).

Results

Baseline Characteristics

We identified 280 patients who had newly diagnosed hormone-naïve mPC. Ten patients were excluded from the analysis (eight patient records were unavailable and two patients had chemotherapy in the hormone-resistant setting). The diagnosis was confirmed by either biopsy and/or PSA greater than 100ng/ml with abnormal DRE in 238 patients (88.2%). Of the

270 patients analysed, 103 (38.1%) had at least one cycle of docetaxel and 167 patients (61.8%) had ADT alone. Patients who had chemotherapy were significantly younger and the majority had a performance status of 0 or 1 (Table 1). Patients who had chemotherapy had a significantly higher median PSA. There were no significant differences between the two groups in terms of NLR, and pre-ADT ALP. 19.2% of patients treated with ADT alone were anaemic, compared to 6.7% in the docetaxel group (Chi-sq p=0.005). Performance status was unknown in 31.7% of patients who had ADT alone. There was no histological diagnosis in 85 patients (31.5%), the majority of which was in the ADT alone group, as this group had fewer biopsies than the chemotherapy group.

Treatment characteristics

The majority of patients in both groups received luteinizing hormone-releasing hormone (LHRH) agonists as ADT (Table 2). 83 patients (80.6%) who received docetaxel completed all six planned cycles. 68 patients (66.0%) had no dose modifications throughout the programme of chemotherapy, 30 patients (29.1%) needed one dose reduction and five patients (4.9%) required two dose reductions. 85 patients (82.5%) had no chemotherapy delays.

Safety

There were two deaths in the cohort of patients receiving docetaxel chemotherapy. One patient died from neutropenic sepsis after the sixth cycle of chemotherapy, and the other

was found dead at home after four cycles having declined admission to hospital whilst neutropenic 24 hours prior. 16 patients (15.5%) had four cycles of chemotherapy or less (Table 3). Infections (neutropenic, or non-neutropenic) accounted for 50% of early stoppages. 35 patients (34.0%) needed to be hospitalised during the course of chemotherapy, and for 17 patients (16.5%), this was due to febrile neutropenia. The risk of febrile neutropenia was on average nine times greater in those patients who started chemotherapy within 20 days of starting ADT compared to those who had started chemotherapy 80 days after commencing ADT (Table 4).

Efficacy

The time taken to reach PSA nadir was approximately 7 months for both patients who received chemotherapy and those who received ADT alone (HR 1.07, 95% CI 0.80, 1.42, log-rank test p=0.665), Figure 1.1). Patients who received chemotherapy were more likely to have a nadir value of <0.2 compared to ADT alone (27 patients (26.2%) and 15 patients (8.9%) respectively, Chi-sq test, p=0.001). The chemotherapy group had a significantly longer time to biochemical progression, with the ADT alone group having a hazard ratio of 2.03 for progression (95% CI (1.27, 3.25), log-rank test, p= 0.002, Figure 1.2). Patients who received ADT alone had a hazard ratio of 5.88 for death (95% CI 2.52, 13.72, log-rank p=0.001, Figure 1.3) compared to the chemotherapy group. Median overall survival has not yet been reached in either group. The minimum follow-up for the patients in this cohort from diagnosis was six months.

Discussion

The data presented here are the largest series of real world information on the efficacy of docetaxel in men with newly diagnosed prostate cancer. Following the STAMPEDE data presented in ASCO 2015, it was adopted as the standard of care in the West of Scotland for those patients who were deemed fit for chemotherapy. These data show that less than 40% of all newly diagnosed mPC patients were commenced on chemotherapy. 80% of patients completed all six cycles. Over a third of patients were hospitalised during their treatment and the febrile neutropenia rate was 16.5%. Interestingly, the risk of neutropenic sepsis falls dramatically with increasing time from the start of ADT. Median overall survival has not yet been reached, but the rate of biochemical progression is significantly less in the chemotherapy arm.

The first randomised controlled trial that reported on the use of docetaxel in the hormone-naïve setting was the GETUG-AFU 15 study, which compared ADT alone (n=193) against up to 9 cycles of docetaxel plus ADT (n=193). The median survival for docetaxel plus ADT was 58.9 months, compared to 54.2 months with ADT alone (HR 1.01, 95% CI 0.75, 1.36, not significant). However, there was a significant improvement in biochemical progression free survival in favour of chemotherapy plus ADT (22.9 months against 12.9, p=0.005). Four patients (2.1%) died in the chemotherapy arm, two from infections while neutropenic (Table 5). The trial management group amended the protocol to administer G-CSF with chemotherapy and after this change there were no more fatalities. The WOSCAN data demonstrate a similar mortality rate and this is a concern given that these patients would have expected to have experienced several years of disease control with ADT alone. There

is some disparity between the rate of febrile neutropenia and mortality, which highlights that neutropenia is not the only contributory factor. The rate of febrile neutropenia was similar to the experience from the Velindre cancer centre [8] which reported a rate of 20%.

CHAARTED and STAMPEDE are two landmark studies that demonstrate a survival advantage with docetaxel in this setting. CHAARTED compared 6 cycles of docetaxel plus ADT (n=397) against ADT alone (n=393) and showed an overall survival benefit of 13.6 months (median OS 57.6 against 44.0 months respectively, HR for death 0.61 (95% CI, 0.47 – 0.80, p<0.001)). There was one chemotherapy related death in this trial and the use of G-CSF was as per investigator preference. The largest of these studies is STAMPEDE which included patients with metastatic disease and with high risk locally advanced cancer. STAMPEDE is a multi-arm multi-stage trial which specified six cycles of chemotherapy plus ADT in Arm C (n=592), and with the addition of zoledronic acid in Arm E (n=593). This showed a 10 month overall survival benefit with ADT and chemotherapy (median OS 81 against 71 months in the ADT alone arm, HR 0.78, 95% CI 0.66-0.93, p=0.006). The addition of zoledronic acid had no effect on survival. The median time from commencing ADT to starting chemotherapy was 8 weeks.

We demonstrated a significantly increased risk of febrile neutropenia in patients who started docetaxel within 20 days of commencing ADT. The increased toxicity may be related to decreased docetaxel clearance in non-castrate men, independent of CYP3A4 activity, possibly due to alteration in the number and function of docetaxel transporters in the liver [9]. One putative mechanism of our finding is that the change in the hepatic transport proteins occurs over several weeks, and so patients who start sooner have a greater

exposure to docetaxel. Alternatively, patients with mPC are likely to have significant bone marrow infiltration, therefore less able to recover after cytotoxic chemotherapy. After several months of androgen suppression however, the disease burden in the bone marrow is less, and therefore is better able to maintain neutrophil counts when challenged with docetaxel. A third possible factor is the effect of androgen deprivation on neutrophil development and maturation. In mice studies, the androgen receptor is essential for neutrophil production [10], and it is possible that ADT in humans may have some effect on this process, although further evidence is required.

The median time from commencing ADT to the start of chemotherapy was 1.2 months in CHAARTED and 2 months in STAMPEDE, which suggests that the efficacy of docetaxel is preserved if chemotherapy is started later. The relationship between time from ADT to chemotherapy and neutropenic sepsis requires further validation with the larger trial datasets. Given the high rate of febrile neutropenia, and its subsequent effect on treatment related deaths and early cessation, delaying the start of chemotherapy for at least 3 weeks after starting ADT should be considered. Guidelines on G-CSF use suggest using primary prophylaxis at a febrile neutropenia rate of greater than 20%, which is higher than 16.5% we observed [11]. However, the mPC population tend to be older and have more co-morbidities hence are less likely to cope with the physiological demands of neutropenic infections. Therefore G-CSF should be considered in those patients particularly at risk as a pragmatic measure.

Approximately 40% of patients with treatment-naïve mPC proceeded to chemotherapy. This uptake is lower than expected, especially given a recent survey showing that 96% of uro-

oncologists would prescribe docetaxel to patients with newly-diagnosed mPC [12]. Our data show that older patients and those with poor performance status were less likely to receive chemotherapy. It is possible that patients in these categories are less likely to be referred for oncological opinions leading to a false impression about the proportion of patients getting chemotherapy in routine oncological practice. Of note, our data included *all* patients with metastatic disease at diagnosis and not just those who presented to oncologists. Other possible reasons for this low uptake may be due to comorbidities that preclude chemotherapy (which were not accounted for in this study), or systemic issues regarding adopting new guidance through a cancer network.

Although the STAMPEDE data included all patients with metastatic disease, pre-planned subgroup analysis of the CHAARTED trial suggested some uncertainty about the value of chemotherapy in patients with 'low volume' metastatic disease (defined as patients with less than four bone metastases, with none outside the vertebral bodies or pelvis and no visceral metastases). Our methodology did not permit us to explore the relationship between volume of disease and likelihood of receiving chemotherapy so, although regional guidelines recommend chemotherapy for all suitable patients with metastatic disease, it is possible that some of the lower than expected uptake was due to less use in patients with low volume disease.

The patients who had docetaxel and ADT had a significantly lower risk of death, which is partially due to the patients in this group being younger and of better performance status. The duration of follow-up of this cohort of patients is too short to ascertain if the overall survival gain demonstrated in STAMPEDE and CHAARTED can be reproduced outside of a

clinical trial. However, our data regarding biochemical progression appears similar
The limitations of this study are that the patients were drawn from a wide geographical area, therefore the recording of key characteristics such as performance status were incomplete in the ADT alone group. The reasons why patients did not have chemotherapy were difficult to ascertain as was the cause of death. Chemotherapy toxicities that did not result in a dose reduction were less reliably recorded.

The strength of this study is that it comprehensively captures nearly all newly diagnosed patients over the first year of docetaxel use in clinical practice in WoSCAN, and provides robust data on the haematological toxicities and rate of hospitalisation and death. These data highlight the significant risks of chemotherapy in this population and the need to consider additional measures to reduce this.

In conclusion, the safety and efficacy of first-line docetaxel in mPC are comparable to the clinical trials. There was a nine-fold increase in risk of febrile neutropenia if chemotherapy was started within 20 days of commencing ADT. The administration of G-CSF or delaying starting chemotherapy for at least three weeks after ADT should be considered to reduce this risk, and improve the safety of a proven life-extending intervention.

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Conflict of Interest Submission

Regarding the work under consideration for publication, there are no conflicts of interest for any of the authors.

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Regarding intellectual property, patents and copyrights, there are no conflicts of interest for any of the authors.

No authors declared any other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what was written in the submitted work.

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Diagnosis of Advanced Prostate Cancer - Revolution or Evolution? Findings from a British Uro-oncology Group UK Survey to Evaluate Oncologists' Views on First-line Docetaxel in Combination with Androgen Deprivation Therapy in Castrate. Clin Oncol [Internet]. 2016;28(6):376–85. Available from: http://dx.doi.org/10.1016/j.clon.2016.01.006

		Chemo + ADT (n=103)	ADT alone (n=167)	
Median age (range)		68 (45-85)	81 (46-98)	*p=0.001
Age (%)	*<70*	59 (57.3)	21 (12.6)	
	≥70	44 (42.7)	146 (87.4)	
Performance status (%)	*0*	60 (58.3)	9 (5.3)	*p=0.001
	1	40 (38.8)	38 (22.8)	
	2	3 (2.9)	49 (29.3)	
	3	0	18 (10.8)	
	Unknown	0	53 (31.7)	
Sum Gleason Score (%)	*6-7*	23 (22.3)	20 (12.0)	
	8-10	65 (63.1)	56 (33.5)	
	Unknown	15 (14.6)	91 (54.5)	
Median PSA (range)		218.5 (3-10353)	141 (1-5412)	*p=0.006
NLR	*<3*	70 (68.0)	90 (53.9)	p=0.454
	>3	33 (32.0)	77 (46.1)	
Alkaline Phosphatase (%)	*<1.5 ULN*	67 (65.0)	103 (61.7)	p=0.508
	≥1.5 ULN	35 (34.0)	64 (38.3)	
	Unknown	1 (1.0)	0	
Haemoglobin (%)	*<110*	7 (6.8)	32 (19.2)	*p=0.005
	≥110	95 (92.2)	134 (80.2)	
	Unknown	1 (1.0)	1 (0.6)	

Table 1. Baseline characteristics

		Chemo + ADT (n=103)	ADT alone (n=167)
Type of ADT (%)	*LHRH agonist*	71 (69.0)	96 (57.5)
	Degarelix	26 (25.2)	62 (37.1)
	Other	6 (5.8)	9 (5.4)
No. of cycles (%)	*1*	5 (4.9)	-
	2	4 (3.9)	-
	3	4 (3.9)	-
	4	4 (3.9)	-
	5	4 (3.9)	-
	6	83 (80.6)	-

Table 2. Treatment characteristics

	n (% of all docetaxel patients)
Febrile neutropenia	4 (3.9)
Non-neutropenic infections	4 (3.9)
Neurotoxicity	2 (1.9)
Not tolerated	1 (1.0)
Diarrhoea	1 (1.0)
ALT/AST elevation	1 (1.0)
Interstitial pneumonitis	1 (1.0)
Pulmonary embolism	1 (1.0)
Death	1 (1.0)

Table 3. Reasons for stopping chemotherapy at 4 cycles or less. ALT, Alanine transaminase. AST, Aspartate transaminase.

Days from starting ADT to starting chemotherapy	Neutropenic events	Number of patients at risk	Odds ratio of febrile neutropenia	
0-19	3	7	9.75	(1.22,77.72) p=0.032
20-39	4	17	4	(0.65,24.77) p=0.136
40-59	4	26	2.95	(0.52,16.76) p=0.221
60-79	4	25	1.86	(0.28,12.16) p=0.519
>79	2	28	1 (reference)	-

Table 4. Odds ratio of events of febrile neutropenia against time from starting ADT to 1st dose of docetaxel.

	STAMPEDE (Arms C+E, n=1185)	CHAARTED (n=397)	GETUG-AFU-15 (n=192)	WoSCAN (n=103)
Treatment related deaths	0.7%	0.2%	2.1%	1.9%
Rate of febrile neutropenia	14-15%	6%	4.1%	16.5%
Grade 3-4 toxicity/hospitalisation	52%	16.6%	37.3% (approx)	34%

Table 5. Safety profile of ADT and docetaxel in WoSCAN compared to similar RCTs

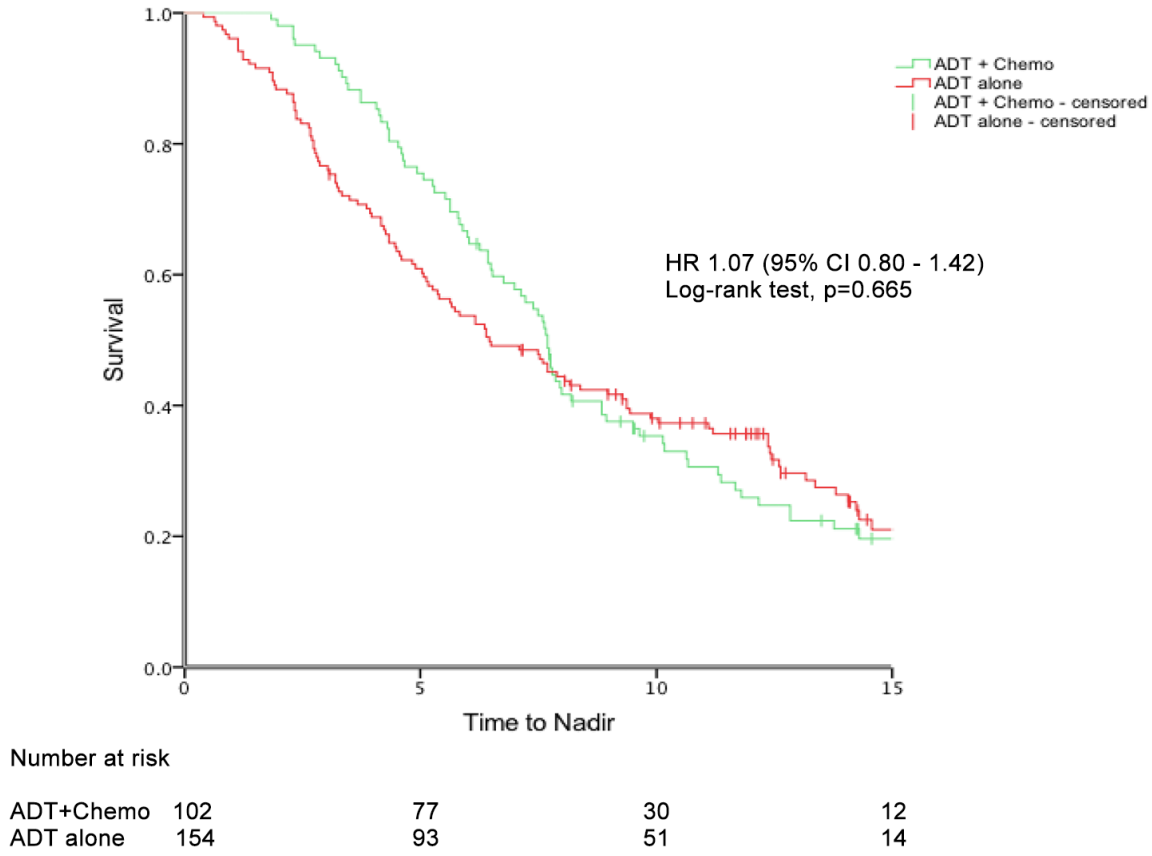

Figure 1.1 Kaplan-Meier plot for time to nadir. Median time to nadir was 6.5 months in the ADT alone group, compared to 7.8 months in the chemotherapy group.

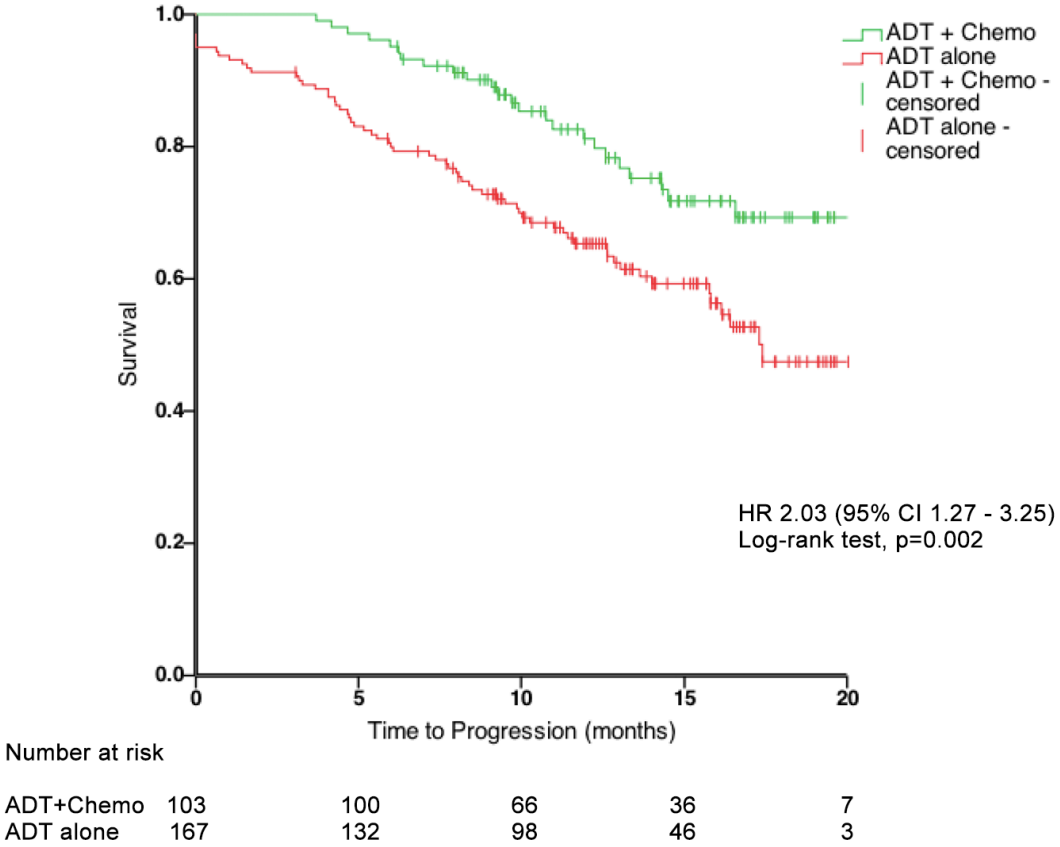

Figure 1.2. Kaplan-Meier plot for time to progression. Median time to progression was 17.2 months in the ADT alone group, and was not reached in the chemotherapy group.

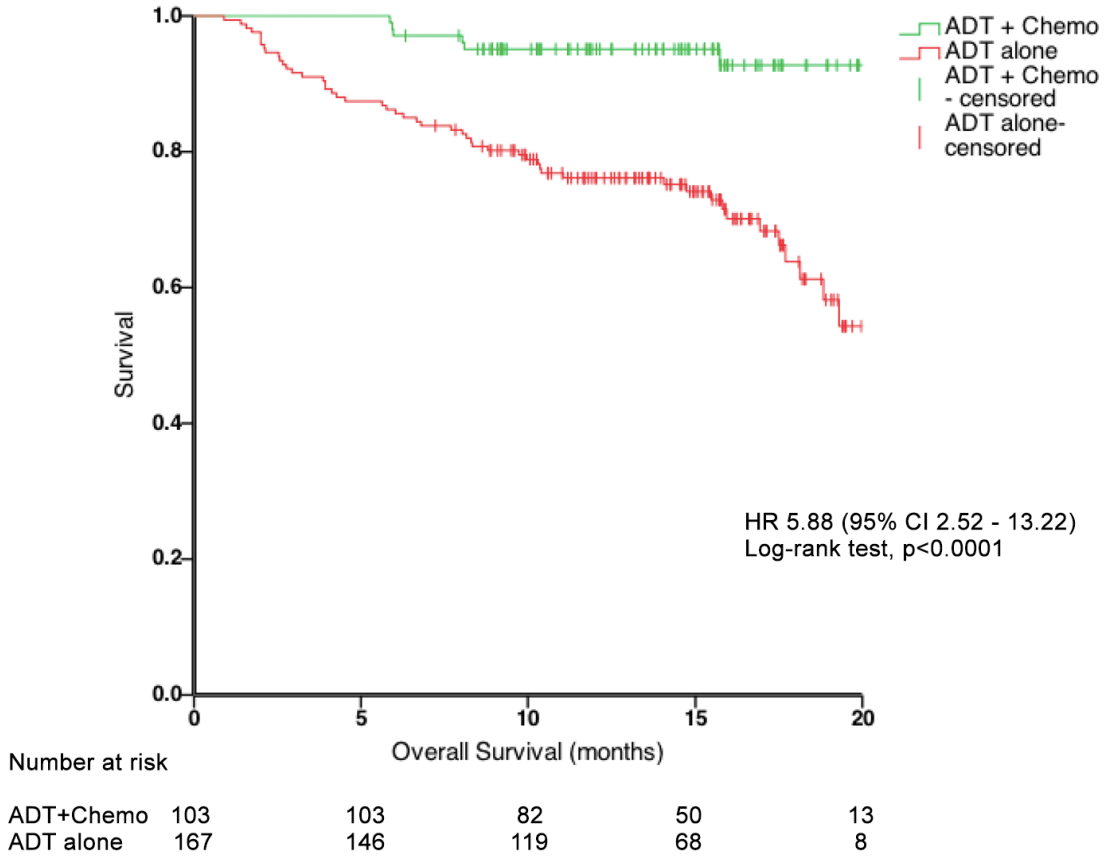

Figure 1.3. Kaplan-Meier plot for overall survival. Neither group reached median survival.