Obesity as a predictor of biochemical recurrence and survival after radiation therapy for prostate cancer

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INTRODUCTION

Obesity has been increasingly identified as a major health concern in Canada and the United States. The percentage of overweight men (BMI > 25 kg/m²) in Canada increased from 47% in the 1970s to 58% in the 1990s [1]. Obesity has been related to an increased risk of cancer, particularly cancers with a hormonal basis such as breast, prostate, endometrium, and colon [2]. In addition, in a large study of over 900,000 American adults, increased body weight was associated with an increased risk of death from a number of cancers, including a relative risk of death from prostate cancer of 1.34 for obese men, compared to normal weight men [3].

In patients with prostate cancer undergoing radical prostatectomy, obesity has been associated with higher grade disease, positive surgical margins, extraprostatic extension, and lymph node metastases in different studies [4–6]. In addition, BMI has been associated with an increased risk of biochemical progression after radical prostatectomy in a number of large studies [4,5,7], although this relationship has not been universally demonstrated in all such studies [6].

The relationship between obesity and clinical outcomes after radical RT for prostate cancer is uncertain. One study of patients undergoing RT found that obesity independently predicted biochemical and clinical failure [8]. To our knowledge, no reported data exists that examines the relationship between obesity and survival outcomes after RT. The objective of this study was to determine if obesity was associated with adverse pathological features at diagnosis, reduced bDFS, DSS, or OS after RT.

PATIENTS AND METHODS

The initial patient data set comprises 909 men with Stage T1–T4 N0/X M0/X prostate adenocarcinoma treated in British Columbia with RT between January 1, 1994 and January 1, 2001. The cutoff date was chosen to allow potential minimum follow-up of five years. No patient received neoadjuvant or adjuvant androgen deprivation therapy (ADT). Institutional ethics approval was obtained for this study.

The BC Cancer Agency (BCCA) maintained a prospective database of prostate cancer patients treated with radical RT, and the only criteria for entry into the database is the...
proximity of the patient to a cancer center and the willingness of patients to attend regular follow-up at one of the BCCA cancer centres. The database contains information on patient factors (e.g. age, co-morbidity, etc), tumour factors (e.g. initial PSA, stage, grade, etc) and treatment factors (e.g. use and duration of ADT, radiation dose etc). Patients are followed according to a standardized follow-up: visits at six weeks post RT, then every six months for three years then annually. At each visit a history and physical are performed, along with a PSA, testosterone, and tumour control and toxicity scoring. Additional investigations are undertaken if clinically indicated. All data except heights and weights was collected prospectively and entered into the database.

Height and weights were retrospectively collected by chart review, and were generally measured by a clinic nurse at the time of first visit. Values were included if measured prior to radiotherapy (97.7% of men) or within six months of initiation of radiotherapy if pre-RT values were not measured (2.3%), and were available for 706 men. BMI was calculated using the formula: BMI = [weight (kg)]/ [height (m)]². Patients were categorized as obese (BMI ≥ 30 kg/m²), overweight (BMI 25–29.9 kg/m²) or normal-weight (BMI 18.5–24.9 kg/m²). All three patients who were underweight (BMI < 18.5 kg/m²) were included in the normal-weight category. Twenty-six patients who were morbidly obese (BMI ≥ 40 kg/m²) were included in the obese group, except for one exploratory analysis in which they were analyzed separately, as indicated below.

Of the 706 patients analyzed, 326 (46%) were diagnosed with prostate cancer by screening (PSA or digital rectal examination), whereas 297 (42%) were detected based on symptoms, and the method of detection was unknown for 83 (12%). The screening-detected patients did not differ from symptomatic patients in terms of age (p = 0.47), BMI (p = 0.74), Gleason score (p = 0.47), stage (p = 0.37), or PSA at diagnosis (p = 0.48).

Patients were CT planned and treated with photon irradiation. Three-dimensional conformal therapy was used beginning in 1998. The median prescribed dose was 66 Gy, and 12% of patients were treated with a hypofractionated regimen to a total dose 52.5 Gy, many as part of a clinical trial. The last date of radiotherapy was taken as day 0 of follow-up. Biochemical relapse was defined by the Phoenix definition, as a rise in PSA by 2 ng/mL above the nadir value [9,10]. Prostate cancer specific death was determined by a review of death records. Internal database checks were carried out by algorithms looking for unlikely clinical scenarios (such as a death coded as disease-specific, but with a low PSA) which were resolved by chart audit.

Patients were staged according to the 1997 American Joint Committee on Cancer guidelines. Patients were classified into risk groups (low risk: Gleason ≤ 6; PSA < 10, stage ≤ T2a; intermediate risk: Gleason 7 or PSA 10–20 or stage T2b; high risk: Gleason ≥ 8 or PSA > 20 or Stage ≥ T3), as defined by Canadian Consensus Criteria [11]. In patients who had a biochemical relapse, initiation of salvage hormones was at the discretion of the treating oncologist.

STATISTICAL ANALYSIS

The association between BMI and other pre-treatment risk factors was assessed using Chi-square and ANOVA tests. Kaplan-Meier and a backwards-stepwise Cox regression multivariate analysis were used to evaluate if BMI and other pre-treatment risk factors were associated with bDFS, DSS, and OS. BMI was analyzed as a categorical variable (normal weight, overweight and obese, defined above), as were Gleason score (<6 vs. 7 vs. 8–10) and tumor stage (T1 vs. T2 vs. T3 vs. T4). Pretreatment PSA was examined as a continuous variable after a logarithmic transformation. Post-treatment PSA doubling time (PSA-DT) was calculated from the slope of the logarithmic linear regression line using PSA values greater than 1 ng/mL until intervention. The slope of the regression line was used for statistical analysis, and PSA-DT was calculated as ln 2 divided by the slope. Although the sample size was determined by the size of the cohort, subject to the above exclusions, a sample size calculation was done a priori to ensure sufficient power. For time to biochemical progression, with an estimated hazard ratio of 1.3 for obese vs. non-obese patients, α = 0.05, β = 0.80, and median time to biochemical failure for the obese group of five years, a sample size of approximately 260 patients was required.

All statistical tests were two-sided, and all statistical analysis was done using the Statistical Package of Social Sciences (SPSS version 14.0, Chicago, Illinois).

RESULTS

The median age at diagnosis was 72 years, and the median follow-up for survival was 7.6 years. 195 men were of normal weight, 358 were overweight, and 153 were obese.

Patient characteristics by BMI category are shown in Table 1. Obesity was associated with a younger age at diagnosis (p = 0.002). The BMI groups did not differ in Gleason score (p = 0.28), pretreatment PSA (p = 0.94), tumor stage (p = 0.70), or pre-treatment risk group (p = 0.82). Obese men had lower serum testosterone levels than overweight or normal-weight men (p < 0.001). Serum testosterone levels were not associated with tumor stage or Gleason score.

The BMI groups did not differ in percentage of relapsed men receiving salvage hormone therapy (71%, 70%, and 72% for normal-weight, overweight and obese men respectively, p = 0.91); nor did they differ in median time to initiation of hormone therapy after PSA relapse (median 12, 13, and 13.5 months respectively, log-rank p = 0.84).

There were 292 biochemical failure events in the whole cohort, with a median time to failure of 96 months. Figure 1A illustrates the survival curves for bDFS by BMI group, with median times to biochemical relapse of 93 months, 88 months, and 84 months for normal-weight, overweight, and obese men respectively (log-rank p = 0.48). A trend for higher-BMI patients to recur earlier was illustrated by an exploratory analysis categorizing the morbidly obese patients (BMI > 35 kg/m²) as a separate group, a category used in other studies [4,5,8] (Figure 1B). On univariate analysis, BMI was non-significant in predicting bDFS (p = 0.23). However, on multivariate analysis, BMI was a significant predictor of bDFS (p = 0.02), as was Gleason score (p < 0.001), PSA (p < 0.001), dose (p < 0.001), and tumor stage (p = 0.017).

The groups also differed significantly in post-treatment PSA-DT in patients who experienced PSA relapse. Obese men who relapsed had a PSA-DT of 11 months, compared to 14 months for overweight men.
Obesity was a predictor of DSS, with median times to prostate-cancer specific death of 11.1 years for normal and overweight men, and 10.6 years for obese men (Figure 2, p = 0.01). On multivariate analysis, BMI group remained predictive of DSS (p = 0.008), along with PSA (p = 0.038) and Gleason score (p < 0.001). Dose (p = 0.84), stage (p = 0.55) and age at diagnosis (p = 0.45) did not predict DSS. Overall survival by BMI group is shown in Figure 3. There was a trend toward decreased OS by BMI group (p = 0.058), which persisted on multivariate analysis (p = 0.062). Age at diagnosis (p = 0.03) and Gleason score (p < 0.001) significantly predicted OS on multivariate analysis.

To test the hypothesis that prostate cancer developing in obese men may be less androgen-dependent, we examined prostate-cancer specific survival after initiation of salvage hormones, as an exploratory analysis. On multivariate analysis, the factors predictive of a shorter time from initiation of salvage hormones until prostate-cancer specific death were higher pre-treatment PSA (p < 0.001), and elevated BMI (p = 0.035).

**DISCUSSION**

Obese men with prostate cancer undergoing radical prostatectomy have been shown to have a higher risk of biochemical relapse [4,5,7], and based on a large population study, obese men have a higher risk of dying of prostate cancer [3]. Our study provides
evidence that obese men have inferior outcomes after RT, compared to normal-weight and overweight men.

Obesity was associated with lower pretreatment serum testosterone levels, with obese men having the lowest levels. Obesity is known to be associated with reduced testosterone levels [12], which have in turn been associated with higher grade [13] and stage [14] of prostate cancer. This has led to the hypothesis that lower free testosterone levels may increase the risk for development of more aggressive prostate cancers [15]. However, neither BMI nor testosterone levels predicted tumor grade or stage in this study.

Obese men were diagnosed with prostate cancer at an earlier age than normal-weight and overweight men, a finding which has been previously demonstrated [6–8]. It has been reported that obesity may decrease the rate of prostate cancer detection [16], and yet obese patients were diagnosed at a younger age, suggesting that the evolution of prostate cancer may start earlier, or progress more quickly, in patients who are obese. Alternatively, the pathophysiology of tumors developing in obese men may be different. Further research is needed to address this issue.

This study provides evidence to support the hypothesis that elevated BMI is associated with inferior outcomes after radical RT. Obesity was a significant predictor of bDFS on multivariate analysis, although only a non-significant trend toward reduced bDFS was demonstrated on univariate analysis. These results are concordant with the results reported by Strom et al., [8] who also showed a trend on univariate analysis with significance on multivariate analysis for predicting bDFS.

This study also suggests that obese men have a higher risk of prostate-cancer specific mortality after RT. In addition to demonstrating that BMI predicts DSS on multivariate analysis, we illustrated that obese men have a higher PSA-DT after recurrence. PSA-DT has been shown to be a surrogate marker of prostate-cancer specific mortality after RT or radical prostatectomy [17]. Taken together, these findings provide evidence that obese men have a higher risk of dying of prostate cancer after RT.

A number of explanations have been postulated to account for more aggressive prostate cancer in obese men. Possible mechanisms include dietary factors [18], and alterations in hormonal levels [2,19], such as estrogens, androgens, leptin, and IGF-1, although definitive mechanisms have not been elucidated. Some authors have suggested that lower testosterone levels in obese men may predispose to the development of prostate cancer that is less androgen-dependent [20,21]. In support of this hypothesis, we examined prostate-cancer specific survival after initiation of salvage hormones, as an exploratory analysis, and found that obese men had decreased prostate-cancer specific survival after initiation of salvage hormones. This is compatible with the concept that prostate cancer in obese men may represent a form of early androgen-independent disease. Further studies are needed to clarify the response of prostate cancer to androgen deprivation in obese men.

The conclusions of this study must be considered in the context of its limitations. Height and weight data were retrospectively gathered, and were not available on all patients. We also did not have adequate data on some possible confounding variables, including percent positive cores in many of the biopsy reports, which was not routinely reported during the era of these patients, or medical comorbidities, which may have influenced overall survival. In addition, clinicians may be less likely to treat obese men as aggressively, due to associated comorbidities. Although we did not find any difference in RT dose or initiation of salvage therapy between BMI groups, there may be subtle differences in treatment that could not be detected in this study. This study only included men who did not receive neoadjuvant or adjuvant ADT. The impact of obesity on outcomes for patients receiving neoadjuvant or adjuvant ADT is uncertain.

In conclusion, this study supports the previous literature indicating that BMI predicts inferior biochemical outcomes after RT, and indicates that obese men may be at a higher risk of dying of prostate cancer after RT. Further studies are needed to determine the mechanisms by which obesity affects the natural history of prostate cancer, and whether these differences can be exploited for therapeutic benefit. The growing evidence that obese men with prostate cancer have inferior outcomes also suggests a need for research to investigate if weight loss interventions can decrease the risk of relapse and death in these men.

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CONFLICTS OF INTEREST

None declared.

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