Abstract:

Background:

BC2001, a randomised trial of treatment for muscle-invasive bladder cancer, demonstrated no difference in health-related quality of life (HRQoL) or late toxicity between patients receiving radical radiotherapy with and without chemotherapy. This secondary analysis explores sex-based differences in HRQoL and toxicity.

Methods:

Participants completed the Functional Assessment of Cancer Therapy Bladder (FACT-BL) HRQoL questionnaires at baseline, end-of-treatment, 6 months and annually until 5 years. Clinicians assessed toxicity with the RTOG and LENTSOM scoring systems at the same timepoints.

The impact of sex on patient reported HRQoL was evaluated using multivariate analyses of change in FACT-BL sub-scores from baseline to timepoints of interest. For clinician reported toxicity, differences were compared by calculating the proportion of patients with grade 3-4 toxicities occurring over the follow-up period.

Results

For both males and females all FACT-BL sub-scores had a reduction in HRQoL at end of treatment. For males the mean BLCS score remained stable through to year 5. For females, there was a decline in BLCS from baseline at years 2 and 3 with a return to baseline at year 5. At year 3, females had a statistically significant and clinically

meaningful worsening of mean BLCS score (-5.18 (95% CI -.8.37 to -1.99)) which was not seen in males (0.24 (-0.76 to 1.23)). RTOG toxicity was more frequent in females than males (27% vs 16%, p=0.027).

Conclusion

Results suggest female patients treated with radiotherapy +/- chemotherapy for localised bladder cancer report worse treatment related toxicity in post-treatment years 2 and 3 than males.

Keywords:

Bladder Cancer, oncology, radiotherapy toxicity, quality of life, sex

Introduction:

BC2001 is the largest randomised trial of radiotherapy in muscle invasive bladder cancer conducted to date, demonstrating oncologic benefit when adding chemotherapy to radiotherapy for bladder preservation (1). Results related to the use of reduced high-dose volume radiotherapy, patient reported quality of life outcomes and neo-adjuvant chemotherapy have also been reported (2-4).

There is limited published data on the impact of patient sex on toxicity and health related quality of life (HRQoL) in bladder cancer patients undergoing bladder preservation treatment. One small study showed that urinary function appeared worse in females (5) whilst another showed no difference (6). The main objective of this secondary analysis of BC2001 data was to explore whether sex had an impact on HRQoL and/or long-term toxicity within a large, randomised radiotherapy trial.

Methods

Trial design and participants:

BC2001 is a phase III trial conducted at 45 UK hospitals. The trial randomised patients 1:1 to chemoradiotherapy or radiotherapy alone and/or 1:1 to receive standard whole bladder radiotherapy or reduced high-dose volume radiotherapy with a tumour boost. Full trial design details were previously reported (1, 7).

BC2001 participants were asked to consent to the optional HRQoL study. Patient reported outcomes (PROs) were collected using the FACT-BL questionnaire at baseline (pre-radiotherapy), end-of-treatment, 6 months post-treatment and then annually to 5 years. The questionnaire includes 39 items with a five-point Likert scale and five subscales: physical well-being (PWB), social well-being (SWB), emotional well-being (EWB), functional well-being (FWB) and the bladder cancer subscale (BLCS). The FACT-BL total score (TOTAL, generated from the sum of all the items comprised in PWB, SWB, EWB, FWB and BLCS subscales) and Trial Outcome Index score (TOI, generated as the sum of all of the items comprised in the PWB, FWB and BLCS subscales) were calculated (8). Scoring and management of missing items were dealt with according to the FACIT administration and scoring guidelines (9). For questions within the FACT-BL that were phrased negatively, scoring was reversed, so high scores are indicative of a better quality of life.

Toxicity data was collected by clinicians using the RTOG (Radiation Therapy Oncology Group) and LENT/SOM (Late effects in normal tissues subjective, objective and management) scores. Data were collected at the same timepoints as PRO. The LENT/SOM scale is made up of questions in three domains (subjective, objective and management) graded 1 to 4 depending on severity. Similarly, the RTOG grading systems grade toxicity on a scale of 1 to 4 with 4 being the most severe side effects.

Statistical Analysis:

Baseline characteristics according to patient sex were analysed for differences between groups using t-tests, chi squared tests and chi squared tests for trend as

appropriate. Change from baseline (post radiotherapy score at each timepoint minus the baseline score) was calculated for BLCS, TOTAL and TOI at each time-point of follow up. A negative change score signifies a decline in HRQoL from baseline.

An analysis of covariance (ANCOVA) regression model, adjusting for baseline score, was used to formally test for a difference in HRQoL score according to sex, using a 5% significance level and 95% confidence intervals at each timepoint. Sex effect estimates are also presented adjusted for those baseline characteristics that were statistically significant ($p<0.05$) in a univariate model with QoL score changes at any timepoint. Baseline features explored were age (as a continuous variable), complete or incomplete resection on TURBT, bladder capacity (cm^3), tumour stage and grade (ordinal), WHO performance status (ordinal) and treatment received.

The impact of sex on clinically significant change in HRQoL at an individual level was analysed at each timepoint through the percentage of participants experiencing a minimally clinically significant change, either positive or negative, defined as a three-point change from baseline on BLCS, a five-point change from baseline on TOI or a seven-point change from baseline on TOTAL score (10-12).

Six individual items within the FACT-BL questionnaire were pre-specified for analysis at each timepoint according to clinical rationale of potential disparities between the sexes due to pelvic anatomy: “I am interested in sex”, “I have control of my bowels”, “I have diarrhoea”, “I have trouble controlling my urine”, “I urinate more frequently than usual” and “It burns when I urinate”. Individual grades for each item were cross-

tabulated by sex, and appropriate chi-square tests for trend were used to compare them.

For late toxicity the worst grade of toxicity was summarised for each of; RTOG symptoms, RTOG gastrointestinal (GI) symptoms, RTOG genitourinary (GU) symptoms, LENT/SOM symptoms and LENT/SOM symptoms with and without sexual dysfunction. To avoid interpreting disease symptoms as side effects, late toxicity for both RTOG and LENT/SOM scores were censored 3 months before recurrence, occurrence of a second primary or death. Endpoints were summarised descriptively at each time point presenting frequencies and percentages by male/female. Sex-based late toxicity differences were explored by comparison of the proportion of patients with cumulative grade 3-4 toxicities over five years.

Individual items within the RTOG and LENT/SOM scores were analysed and the proportion of male and female patients with grade 3-4 toxicities for each individual question was described.

Results

Patient population

Of the 452 patients that enrolled in the BC2001 HRQoL sub study, 367 (81%) were male. There were no statistically significant differences in baseline characteristics between the two sexes (Table 1).

Patient reported outcomes:

The number of patients completing the HRQoL questionnaires at each time point are displayed in the appendix.

The mean change in baseline BLCS, TOTAL and TOI scores over time is shown in Figure 1. For both males and females there is a negative change from mean BLCS baseline score to the end-of-treatment score improving after 6 months and returning to baseline levels by 12 months. For males, the mean score stabilises for all follow up time-points until year 5. For females, there is a subsequent decline in HRQoL with a negative change in mean BCLS score from baseline at 2 years, worsening at 3 years, improving at year 4, returning to baseline at year 5.

On univariate analysis the baseline factors of age, WHO performance status and tumour stage were shown to cause a significant difference in change in HRQoL scores for at least one of TOTAL, TOI or BLCS and were therefore included in the multivariate analysis at each timepoint.

The difference between males and females was greatest at 3 years with a mean change in BLCS score from baseline of 0.24 (95%CI -0.76 to 1.23) in males and -5.18 (95% CI -.8.37 to -1.99) in females, giving a statistically significant mean difference of 5.42 (95% CI 2.79 to 8.05) between the sexes (p=0.002), after adjusting for age, WHO performance status and tumour stage. There was no statistically significant difference between sexes in the mean change from baseline in BLCS at any other timepoint, or in TOTAL or TOI score at any timepoint.

The evaluation of clinical significance to these changes is shown in Figure 2. 61% of female patients had a clinically significant worsening of QoL at 3 years compared to 28% of male patients. In year 4, the males and females had similar clinically significant changes.

The responses to individual items in the BLCS subscale are illustrated in figure 3. On review of patient scores at year 3, 4/25 (16%) of females reported to have “quite a bit” or “very much” “trouble controlling my urine” compared to 12/127 (9%) males (P=0.007). Similarly, 2/25 (8%) of females responded that they had “quite a bit” or “very much” “burning when I urinate” compared to 1/121 (1%) of males (P=0.025). There was no evidence of differences in response to the questions “I have diarrhoea”, “I urinate more frequently than usual” and “I have trouble controlling my bowels” between males and females. On review of the item “I am interested in sex”, only 1/25 (4%) of females reported that they were “quite a bit or “very interested” in sex compared to 31/127 (25%) of males. This difference was not statistically significant, and it was noted that the baseline interest in sex varied between males and females (Figure 3).

Clinician reported outcomes

On analysis of clinician reported toxicity, 21/77 (27%) of female patients had an RTOG grade 3 or 4 toxicity (G3+) compared to 54/329 (16%) of male patients (P=0.027) at any time in the five-year follow-up. This remained significant after censoring for recurrence. The difference in toxicity between males and females appeared to be driven by a significant difference in GI toxicity, with 7/77 (9%) of female patients being

described as G3+ at some stage over 5 years in comparison to 12/329 (4%) of male patients (p=0.042). For RTOG GU toxicities 15/76 (20%) of female patients reported G3+ compared to 44/326 (13%) of male patients (p=0.166).

Analysis of G3+over time shows that the greatest level of toxicity appears at year 1, with 6/42 (14%) of female and 3/179 (2%) of male patients having G3+ toxicity at this time. This appears to gradually improve over time. Formal analysis of the discrepancies between males and females as a function of time was not performed as the number of recorded G3+ events was low and did not allow for detailed analysis of individual time points.

Individual domains of RTOG toxicity are presented in table 2. The number of G3+ for each individual domain were low and no statistically significant differences were seen between the two genders.

Using the LENT/SOM scale, 63% of male patients were reported to have G3+ toxicity in six domains (table 3) compared to 49% of female patients (p=0.026). However, when the results were censored for recurrence this difference was no longer statistically significant (p=0.088). This trend towards worse toxicity in male patients in the LENT/SOM score was influenced by the sexual function component of the score with 142/283 (50%) of male patients reported to have G3+ toxicity according to the LENT/SOM scales compared to 9/65 (14%) of female patients (p=0.036), compared to 34% and 6% at baseline. When the overall G3+ toxicity was evaluated without incorporating sexual dysfunction there was no statistically significant difference between males and females. Further analysis of the individual components of the

LENT/SOM score showed females to have a significant increase in G3+ rectal symptoms with 6/70 (9%) of females reporting toxicity compared to males 9/299 (3%) p=0.034. There was a non-significant trend to a higher rate of G3+ toxicity in females rather than males in all other domains (table 3).

Discussion

We previously reported a reduction in HRQoL at the end-of-treatment for patients treated with radiotherapy for bladder cancer which largely improves to baseline levels at 6 months post treatment (3). Here we report that female patients have an additional decline in HRQoL at 2 years post treatment which improves by 5 years. The reason for this trend is unclear, appearing to be related to worsening urinary function in female patients at this time. In the clinician reported outcomes worsening toxicity in female patients is noted in GI function. We can conclude from our data that although patients of both sexes largely recover to baseline levels of function at 5 years post treatment there is a period from year 1-3 where female patients may require more intensive follow up support for toxicity management.

Although literature has previously been published on the long-term toxicity following treatment of bladder cancer with radiotherapy there is limited published evidence as to the role that sex may play (13).

Zietman et al (5) reviewed 71 patients with T2-T4a bladder cancer who had received tri-modality therapy with transurethral resection, chemotherapy and radiotherapy. The study showed that 45% of females reported urinary leaking compared to 11% of males.

Similarly, 25% of females described urinary urgency compared to 11% of males. GI toxicity was varied and although females showed a slightly higher rate of difficulty with bowel control than males (27% vs 20%), males described more abdominal cramping (17% vs 0%), bleeding and tenderness. Only two females completed the sexual function questions and therefore it was not possible for the study to comment on gender difference in sexual function. Similarly, as baseline data was not available for these patients pre-treatment it is possible that these gender differences were in existence prior to treatment.

Our analysis shows an increase in the rate of sexual dysfunction in males using the LENT/SOM score compared to a non-significant trend towards increased sexual dysfunction in females in the FACT-BL score. Historically, there have been difficulties collecting sexual function data for female patients as shown in the Zietman paper, and questionnaires continue to have different questions for males and females. The fact that females appear to have greater sexual dysfunction in the FACT-BL score but better sexual function in the LENT/SOM score could be due to females being more comfortable reporting symptoms in patient reported outcome questionnaires compared to potential underreporting in consultations with clinicians. Similarly, the potential different sexual expectations of males and females shown by the differing baseline interest in sex in both the FACT-BL and LENT/SOM scores may account for these differences.

The inclusion of sexual dysfunction in the LENT/SOM significantly increases the rate of overall G3+ toxicity in males in comparison to the RTOG clinician reported outcomes which do not evaluate sexual function. When the LENT/SOM score analysis

is run without sexual dysfunction there is shown to be a consistent reduction in female quality of life in both clinician and patient reported outcomes.

A later study of long-term toxicity in patients treated with trimodality therapy for T2 to T4a bladder cancer (6) was undertaken. Patients were included in the analysis if they had survived two or more years post treatment, had a native bladder and were treated with radical radiotherapy to the bladder. The worst grade of toxicity reported for each patient >180 days post treatment was recorded. Of 157 analysable patients 82% were male, 7% of patients reported a grade 3 pelvic toxicity with no difference between men and women (OR 0.98 (95% CI 0.20-4.79) p=0.98). It is possible that this study underestimated the grade of toxicity experienced by the patients in comparison to the study by Zietman and our data from the BC2001 trial as a result of using only clinician reported outcomes.

By comparison, reported differences in HRQoL between males and females following cystectomy are also limited. Smith, et al conducted a systematic review of urinary, sexual and bowel function along with overall HRQoL among women who underwent radical cystectomy (RC) and found that published studies are highly limited in their heterogenous patient populations, with limited use of validated questionnaires and small sample sizes. What they did report was that sexual function was better in those undergoing genitalia-sparing RC and that compared to the general population (14). In a direct comparison of men and women in a patient population who underwent ileal conduit reconstruction following RC, female patients had greater problems than men in cognitive functioning and future perspective, while men had more problems with sexual functioning than women (15).

Bladder cancer is more common in males and this is reflected in our cohort by the relatively small number of females. Despite this, our study provides one of the largest sets of data in females. Strengths of our study include the prospective and longitudinal collection of data from a pre-treatment baseline, mitigating against recall bias and allowing evaluation of changes over time, and of both patient and clinician reported outcomes.

Reasons for worsening urinary function in females are unclear, and further evaluation would be required to establish whether there were changes in dosimetry due to anatomical differences. Alternative possibilities requiring further evaluation would include whether the differences seen could be related to the expectation of treatment toxicity or perception of side effects between genders.

Conclusion

Results from this exploratory analysis of the BC2001 trial suggest that female patients treated with radiotherapy +/- chemotherapy for localised bladder cancer report a worse treatment related toxicity than males during follow up. However, this disparity resolves by 5 years post treatment.

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