Dose-Volume Predictors for Patient-Reported Late Diarrhoea, Faecal Incontinence and Urgency after Pelvic Radiotherapy

Introduction

The use of pelvic radiotherapy for urological, gynaecological and colorectal cancers continues to rise, with an associated increasing number of survivors (1). However, this increase in cure rates comes at a cost for many patients. It is estimated that 50% of pelvic cancer survivors will have lasting bowel toxicity that will impact their quality of life (2). In particular, bowel symptoms of faecal urgency, diarrhoea and incontinence which may occur after pelvic radiotherapy can be socially debilitating, affecting quality of life in up to 79%, 67% and 79% of patients respectively (3).

In the last two decades, centres worldwide have adopted advanced radiotherapy techniques such as intensity-modulated radiotherapy (IMRT). In the context of pelvic radiotherapy the prime aim of such techniques is to reduce bowel toxicity. Despite the effort and resource that has gone into implementation of these techniques, how to make best use of advanced radiotherapy techniques to reduce late bowel toxicity, and specifically those symptoms which negatively impact on quality of life, is unclear.

Dose-volume predictors and constraints in relation to bowel symptoms are traditionally related to two organs at risk (OARs), the rectum and the "bowel". The rectum is a well-researched OAR, and there is significant high quality published data which has allowed the development of dose-volume constraints for the rectum which are widely used (4). The bowel on the other hand is a less researched OAR.

In the early 1990s, Emami *et al* defined dose-volume limits for the bowel, which was mainly based on "expert opinion" and 2-dimensional planning data, not in keeping with current practice (5). Twenty years later, the Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) initiative updated this data with the use of 3-dimensional data. For bowel toxicity QUANTEC focused on "small bowel", and recommended dose-volume constraints which are derived from acute toxicity data (6). The QUANTEC researchers comment that these constraints "may also reduce late toxicity risk, although this correlation is not established". No detailed study of late toxicity was reported in the QUANTEC reviews.

The fundamental questions of: "how much bowel do we need to spare to reduce late bowel toxicity", "to what dose level" and to "which component/definition of bowel" remain currently unanswered. Only when we have some answers to these questions can we really make best use of advanced techniques to reduce distressing symptoms for our pelvic cancer survivors.

To evaluate this further, we undertook a systematic review of the published data on non-rectum dosimetric predictors of late bowel toxicity (7). Despite 30 studies (including 5136 patients) being included, many studies were inconclusive, and there was methodological variation, with differing toxicity endpoints and definitions of bowel. Some studies examined bowel loops (where individual loops are outlined), others bowel bag/peritoneal cavity (the potential space for where mobile bowel may be positioned over a radiotherapy course). Further studies defined bowel as small bowel, large bowel, or individual components such as duodenum, sigmoid or anal canal.

The most conclusive studies (8-11) included the anal canal as an OAR, and we concluded that using Dmean<40Gy to the anal canal is likely to reduce risk of late faecal incontinence. These studies generally used precise and consistent methodology and the results could be corroborated between studies. From the remaining studies there were promising findings for bowel loops, small bowel, sigmoid and large bowel (12-16), however no recommendations could be made as these findings could not be validated or corroborated between studies, due to different definitions of bowel and toxicity.

This study aims to establish dose-volume predictors for patient-reported late bowel toxicity. Given their impact on quality of life we have focussed on three symptoms: faecal urgency, faecal incontinence and diarrhoea. We aim to define our own dose-volume constraints for these toxicities, and to corroborate constraints in published literature.

Methods and Materials

Patient population

Between September 2012 and 2014 all patients who had radical or adjuvant pelvic radiotherapy for cervical, endometrial, bladder and high-risk prostate cancer (where pelvic nodes were treated) were included. Patients were treated with a variety of 3D-conformal radiotherapy, fixed-field IMRT or VMAT. A range of different dose-fractionations relevant to each tumour site, using dose-volume constraints and objectives from our institutional protocols were used. Concurrent chemotherapy was used for some cervical and bladder cancer patients, and brachytherapy was used for cervical and endometrial cancer patients.

Toxicity data collection and endpoint analysis

Eligible patients were sent subjective component of the LENT-SOMA scales (17) patient questionnaires via post at two time points. For the main assessment a first time point of 12 months after completion of radiotherapy was used, and for further internal validation a second questionnaire was sent at the 24-month time point to those who responded initially. Completed questionnaires were returned via freepost.

In the absence of baseline scores, one additional question was added: “are any of the symptoms you report longstanding, i.e. started prior to radiotherapy?” with a free text space to allow patients to comment.

Data for faecal urgency, incontinence and diarrhoea were analysed. For each of these symptoms two endpoints were collected: the presence versus absence of the symptom (any grade); the presence versus absence of high grade (grade 3-4) toxicity. Patients who reported symptoms prior to radiotherapy were excluded from analysis.
Potential confounding factors were recorded. This included patient-related factors (age and gender), disease-related factors (disease site, stage) and treatment-related factors (total dose fractionation, pelvic dose/fractionation, fraction size, radiotherapy technique, and use of chemotherapy, brachytherapy and hormones).

OAR definitions and DVH data collection
For each patient who returned a fully completed questionnaire, their planning CT was retrospectively contoured to include the following 6 definitions of bowel: bowel bag, bowel loops, small bowel, large bowel, sigmoid and anal canal. OARs were defined (see table 1) with the use of RTOG guidance (18), and with guidance from our in-house GI radiologist. 4.2cm above the planning target volume (PTV) was chosen as it was noted that low dose was still found 3cm above the PTV, in order to ensure that all dose (even lowest dose) was considered.

All OARs were outlined by a single outliner with radiology guidance for the first 10 cases. Dose-volume data was extracted with the use of in-house software "DVH Import", and was converted with the EQD2 formula, using an alpha-beta ratio of 3. Dose-volume parameters recorded for each OAR included V5, V10 in 5Gy increments up to V55, as well as Dmax (D0.1), Dmedian, and Dmin. Volume was defined as either absolute (cc) for all OARs, however for those OARs where the whole organ was assessable (sigmoid, rectum) percentage % volume was also analysed.
For gynaecological cancers, the summation of bowel dose from external beam radiotherapy (EBRT) and brachytherapy dose was considered. However, summation was not possible to accurately perform due to positional differences between the CT planning scans of the two treatment stages, which caused the bowel to be in different positions between EBRT and brachytherapy. In view of this, as in other published papers, a pragmatic view was taken to include only doses from EBRT, and to consider brachytherapy as a confounding factor in the statistical model.

Statistical data analysis
All statistical analysis was performed on SPSS20, and was done in two stages:

1. Analysis of dose-volume predictors and constraint derivation
Chi-squared analyses of confounding factors with toxicity were assessed, to determine any significant association with each toxicity.
Binary logistic regression was used to determine the predictive value of the dose-volume parameters towards the toxicity endpoints. First a univariate analysis (UVA) was performed, and for significant parameters (defined as $p<0.2$ on UVA), a multivariate analysis (MVA) was then carried out. Significant confounding factors found from the initial Chi-squared analysis

were included in the model for MVA. The MVA used was a backward-stepwise regression analysis which was chosen as it eliminates non-significant variables, taking into account multiple hypothesis testing and avoiding the need for Bonferroni corrections. The odds ratio (OR) and confidence interval (CI) for each positive parameter was noted. Significance level for MVA was $p<0.05$.

Constraints were derived for each dose-volume parameter that was positive on MVA, with the predictive probability from the logistic regression plotted against the volume of the OAR. Toxicity rates above and below each constraint were assessed and if these rates were significantly different (determined by Pearson's chi-squared testing, $p<0.05$) these were classed as having a "good fit" to the data and were included for further assessment.
The constraints derived were scrutinised further with the following assessments:

- Clinical value: if the toxicity rate below the constraint was >25% these constraints were disregarded
- Accuracy: specificity and sensitivity rates
- Discriminatory value: using AUC statistics
- Validation with toxicity data at 24 months: data re-explored to assess if the constraints still discriminate at 24 months, with Pearson Chi-squared analysis for goodness of fit.

2. Application of published dose-volume constraints to dataset

Table 2 shows the important dose-volume constraint found in our systematic review.
Each constraint was applied to our current dataset, to determine if they dichotomised patients with and without toxicity.

Results

Patient and treatments characteristics

226/306 (73.9%) patients returned questionnaires at the 12-month time point, and 203 of these questionnaires were complete. For validation these 203 patients were sent a further questionnaire at the 24-month time point. By the time of the current analysis, 151 patients were sent a questionnaire at the 24-month time point, of which 105 (69.5%) returned evaluable questionnaires.

Table 3 details the characteristics of the 203 patients used for analysis at the 12-month time point. There was a predominance of prostate cancer patients. Fifteen different dose-fractionation schedules were used (figure 1), the most common being 60Gy/20# and 74Gy/37# reflective of prostate cancer treatments in our centre between 2012-14.

Toxicity Analysis

Faecal urgency was reported by 100/203 (49.3%) of patients, with 82/203 (40.4%) reporting high grade urgency. 42/203 (20.7%) reported faecal incontinence (6/203 (3%) high grade) and 37/203 (18.2%) reported diarrhoea (3/203 (1.5%) high grade).

For all 3 symptoms toxicity rates decreased from 12 months to 24 months, yet this was not statistically significant (figure 2).

Younger patients (below median of 70 years) reported a higher frequency of incontinence 33.3% for younger patients, versus 15.3% for older patients (p=0.005)), and diarrhoea (30.1% versus 8.6%, (p=0.001)). Patients treated with IMRT or VMAT had a higher frequency of incontinence compared with conformal radiotherapy (34% compared with 19%, p=0.04). Tumour site, use of concurrent chemotherapy, brachytherapy or hormone therapy had no significant association with the late toxicities studied.

Determination of dose-volume predictors and constraints

Table 4 summarises the results of the significant dose-volume parameters that showed significance on MVA and the derived constraints. Eleven dose-volume parameters were statistically significant on MVA, and from these 19 statistically significant constraints were derived. Fourteen of these constraints related to the sigmoid colon or large bowel. The relationship of diarrhoea to both bowel bag and large bowel is shown in figure 3, further relationships are demonstrated in supplementary data appendix.

Although all were statistically significant, 10 constraints had less clinical value (toxicity rates remain 25% below the constraint) and were disregarded (shaded grey on table 4), leaving 9 considered to be more clinically valuable. Further analysis of these 9 constraints in terms of accuracy, discriminatory value, and internal validation at 24 months are detailed on the right hand columns of table 4. Eight of these 9 constraints were associated with lower toxicity rates at 24 months in the group below the cut-off compared to the patients above the cut-off.

Application of published dose-volume constraints to current dataset

The published constraints using 'bowel loops' by Guerrero-Urbano et al (12) showed applicability in our dataset. The V45<71cc especially dichotomised our patients with faecal incontinence (32.6% above this constraint vs 14.6% below the constraint, p=0.006), diarrhoea (24.5% to 13.2%, p=0.046), and faecal urgency (59.4% to 41.9%, p=0.015).

For all other published constraints, including the QUANTEC recommendations, when applied to our dataset they did not dichotomise patients with and without toxicity. Full details of this are supplemented (Appendix A).

Discussion

Radiotherapy has a key role in the management of pelvic tumours, either as a curative or adjuvant treatment. The aim of advanced pelvic radiotherapy techniques is to improve both short- and long-term outcomes, with reduction of bowel toxicity being a prime aim.

In the radiotherapy planning process dose-volume constraints are used to optimise radiotherapy plans based on knowledge of dose-volume predictors of specified toxicities. However, the relative sparsity of the dose-volume predictors and constraints for late bowel

toxicity has made it difficult to make best use of these new techniques with certainty of patient benefit.

In this study, with the use of prospectively collected patient-reported outcomes in a heterogeneous group of pelvic radiotherapy patients, we aimed to derive original dose-volume constraints for symptoms which negatively impact quality of life. Key findings were that the sigmoid colon and large bowel are important OARs for the development of late diarrhoea and urgency, and constraints were derived for these.

We found faecal urgency, incontinence, and diarrhoea to be commonly occurring symptoms: 49%, 21%, 18% at 12 months and 45%, 22%, 14% at 24 months, respectively. This is consistent with other published studies (22, 23) where at 12 months urgency was reported in 65-79%, incontinence in 24%, and diarrhoea in 19%. Faecal incontinence is one of the "ALERT-B" questions (24) that is being adopted nationally in the UK as a trigger for referral to specialist gastroenterology service. Knowledge that this symptom is likely to occur in approximately a fifth of pelvic radiotherapy patients is helpful for service planning.

Faecal incontinence was more prevalent in patients treated with IMRT/VMAT treatments, compared with 3D-conformal RT. Diarrhoea and urgency rates were not lower in the IMRT/ VMAT patients either, and this concurs with other published studies (25), where faecal incontinence rates were high 12 months after VMAT (22). However, our study was not designed to detect differences between the techniques, and with only 27% of patients having IMRT/VMAT, the groups were imbalanced. This does highlight however that simply delivering radiation with advanced techniques does not necessarily translate into reduced toxicity for patients, and rigorous audit of our patient-reported outcomes should be performed to determine if and how we are improving outcomes.

We found 8 clinically and statistically relevant constraints for these toxicities, including constraints for bowel bag, bowel loops, sigmoid and large bowel, and 7 of these were validated at a second time point (24 months). Sigmoid and large bowel are rarely considered as OARs in current protocols, and there is a risk that with current protocols focussed on sparing small bowel that increased dose to these structures may be occurring. Interestingly we found no predictive dose-volume parameters for small bowel in our data set.

For diarrhoea, dose-volume parameters to large bowel and to bowel bag were most predictive. The dose-volume-toxicity relationship with these OARs and diarrhoea is demonstrated in figure 3. We suggest the constraints of large bowel V15<60.8cc and bowel bag V5<1689cc to reduce the risk of diarrhoea and recommend they are validated with an external dataset . Of note it was very low dose (5Gy) to the largest OAR (bowel bag) which was found to be important. This may be a pertinent consideration in the current climate with rotational techniques VMAT and tomotherapy being increasingly used. These techniques can

reduce dose to small bowel and rectum, at a cost of increased low dose bath to the rest of the bowel. The consequence of low dose bath on late bowel toxicity is currently not well researched, and our study highlights the need for this.

For faecal urgency, the sigmoid colon had a dose-volume relationship at many dose levels. The constraints Dmedian <13.8Gy to reduce the presence of urgency, and sigmoid V10<52.6% to minimise high grade urgency are recommended for further validation before prospective use. These constraints had high sensitivity, and at the 24 month time point dichotomised patients with and without toxicity, although without statistical significance. There is a growing body of evidence (26-28) for the importance of the sigmoid as an OAR for late bowel toxicity both in EBRT and brachytherapy. Alevronta et al (29) suggest the sigmoid to be a crucial OAR for development of "urgency syndrome" in gynaecological patients, and recommend its routine outlining as an OAR, concurring with our results.

For incontinence, only sigmoid V35<70Gy showed promise at both 12 and 24 month time-points, although others statistical parameters were less encouraging. From our previous systematic review, where we have concluded that anal canal Dmean<40Gy is important to reduce faecal incontinence, this could not be applied to the current data set, as no patients had an anal canal Dmean above this constraint. Regardless of this 23.5% of patients reported faecal incontinence in our study suggesting that development of individual toxicity symptoms is likely to be multifactorial, and not related just to single OAR dose-volume parameters. Sigmoid dose was predictive of incontinence, so we hypothesise it may be a combination of anal canal and sigmoid dose-volume constraints that need to be applied to reduce faecal incontinence.

For all three toxicities our dataset validated the bowel loops constraint V45<71cc by Guerrero-Urbano et al, and this constraint should be mandated to reduce diarrhoea, urgency and incontinence. Given that 63% of our studied patients were a similar patient group to those in Guerrero-Urbano et al's study (high risk prostate cancer where pelvic nodes were treated), this suggests particular applicability of this constraint to this group of patients, although may well be relevant to other tumour sites too.

QUANTEC have recommended the use of constraints of V15<120cc for small bowel loops, and V45<195cc for peritoneal cavity to reduce acute bowel toxicity. These constraints did not dichotomise patients with and without late toxicity in our study, and we conclude should not be assumed to be applicable in both acute and late toxicity scenarios.

This study had many strengths - the data was prospectively collected, patient-reported toxicity from an unselected group of non-trial patients, aiming to assess "real world" toxicity. Our response rate of 74% was high, and the sample size of 203 was larger than most published studies on this subject. A symptom-based approach was adopted, and concerted effort was

made to ensure the data analysis to be as statistically sound as possible, with many of the recommendations from QUANTEC including stating toxicity levels, goodness-of-fit statistics, discrimination and validation being followed.

There were also limitations. Due to time constraints, prospective baseline symptoms scores were not collected, and instead an additional question was used in the questionnaire to determine if symptoms were present prior to radiotherapy, which may under-represent pre-existing symptoms, and there may be recall bias.
It is well known that radiotherapy toxicity is not related to dose-volume parameters alone, and it is crucial to take into account patients co-morbidities such as previous bowel surgery (30) and the presence of inflammatory bowel disease (31), and to consider genetic factors, which were not taken into account in the current study.
As in other key papers such as Emami et al (5), Gallagher et al (32), and the QUANTEC studies (6), the patients within this study were deliberately heterogenous in order to determine constraints that would be clinically applicable for different pelvic clinical scenarios. We aimed to detect the importance of tumour site, brachytherapy, chemotherapy etc. as confounding factors. However, as one tumour site was more dominant (prostate) compared with the others (cervix, bladder, endometrium), the data may be underpowered to detect the impact of these compounding factors, and a more evenly balanced population would have increased confidence in our findings.
Finally, dose-volume data was taken from the "snapshot" planning CT scan, however it is likely that bowel components move during radiotherapy and toxicity may be associated to the accumulated dose rather than the planning dose.

From this work we would strongly recommend prospective clinical use of the constraint for bowel loops (V45<71cc), published by Guerrero-Urbano et al, which we have validated with this data set.
We recommend the validation of the following constraints in external data sets: bowel bag V5<1689cc and large bowel V15<60.8cc to reduce late diarrhoea; sigmoid Dmedian<13.8Gy to reduce the presence of urgency and sigmoid V10<52.6% to reduce high grade urgency. In our future work we would aim to validate these constraints in non-prostate pelvic radiotherapy patients. Outlining of multiple bowel OARs would be impractical and time-consuming and with further study we would aim to pinpoint those OARs where the constraints are most predictive before implementation into clinical protocols.

Conclusion

Late faecal urgency, incontinence and diarrhoea are commonly reported toxicities after pelvic radiotherapy. Along with the more traditionally used OARs such as bowel loops and bowel bag, the sigmoid colon and large bowel are important OARs for development of these toxicities. Constraints for these OARs are proposed to reduce the risk of late patient reported bowel toxicity.

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