Choosing between conventional and hypofractionated prostate cancer radiation therapy: Results from a study of shared decision-making

Thomas P. Shakespeare a,∗, Justin Westhuyzen a, Tracy Lim Yew Fai b, Noel J. Aherne a,c

A R T I C L E   I N F O

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Aim: To evaluate patient choice of prostate cancer radiotherapy fractionation, using a decision aid.

Background: Recent ASTRO guidelines recommend patients with localised prostate cancer be offered moderately hypofractionated radiation therapy after discussing increased acute toxicity and uncertainty of long-term results compared to conventional fractionation.

Materials and methods: A decision aid was designed to outline the benefits and potential downsides of conventionally and moderately hypofractionated radiation therapy. The aid incorporated the ASTRO guideline to outline risks and benefits.

Results: In all, 124 patients with localised prostate cancer were seen from June-December 2018. Median age was 72 (range 50–90), 49.6 % were intermediate risk (50.4 % high risk). All except three patients made a choice using the aid; the three undecided patients were hypofractionated. In all, 33.9 % of patients chose hypofractionation: falling to 25.3 % for patients under 75 years; 24.3 % for patients living within 30 miles of the cancer centre, and 14.3 % for patients with baseline gastrointestinal symptoms. On multivariate analysis, younger age, proximity to the centre, and having baseline gastrointestinal symptoms significantly predicted for choosing conventional fractionation. Insurance status, attending clinician, baseline genitourinary symptoms, work/carer status, ECOG, cancer risk group and driving status did not impact choice. Reasons for choosing conventional fractionation were certainty of long-term results (84 %) and lower acute bowel toxicity (51 %).

Conclusions: Most patients declined the convenience of moderate hypofractionation due to potentially increased acute toxicity, and the uncertainty of long-term outcomes. We advocate that no patient should be offered hypofractionation without a thorough discussion of uncertainty and acute toxicity.

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1. Background

ASTRO recently published a position statement recommending all patients with localised prostate cancer be offered moderately hypofractionated radiation therapy as an alternative to conventional fractionation.1 From a patient perspective the benefit lies in convenience, with fewer visits for radiation. The downsides, as outlined by ASTRO, are the potential for a small increased risk of acute toxicity, and the uncertainty of results beyond 5 years. Many patients are now being offered moderate hypofractionation,2 however the choice of fractionation may often be made by the radiation oncologist without significant input from patients. The authors of the ASTRO statement suggest that the limitations of available evidence “underscore the importance of shared decision-making between clinicians and patients.” In order to facilitate shared decision-making with our patients, we developed a decision aid outlining the two fractionation choices based on the ASTRO consensus statement. We aimed to evaluate our experience using the decision aid, and report on the proportion of patients selecting the two fractionation schedules.

2. Methods and materials

The Faculty of Radiation Oncology Genitourinary Group endorsed the ASTRO Consensus statement in June 2018. As a result, our department developed a decision aid based on the statement to guide our patients in their choice of fractionation schedule. All
patients with localised prostate cancer from mid-June 2018 are now asked to choose their fractionation schedule using the decision aid.

The decision aid was developed using specific recommendations and statements within the ASTRO document, and is shown in Fig. 1. The aid is based on decision aids we have previously developed to help patients decide on fractionation for the treatment of bone metastases and the palliation of lung primaries. The ASTRO consensus guidelines made the following statements which were incorporated into the aid:

1. In men with low-, intermediate- and high-risk prostate cancer receiving external beam radiation therapy (EBRT) to the prostate with or without radiation to the seminal vesicles, moderate hypofractionation should be offered. The task force recommended that moderately hypofractionated EBRT be offered to patients across all risk groups after a discussion of risks and benefits. In patients who are candidates for EBRT, moderate hypofractionation should be offered regardless of patient age, comorbidity, anatomy, or urinary function.

2. To date, there are limited published outcomes beyond five years for moderate hypofractionation. Therefore, current evidence supports similar early cancer control with this approach. However, physicians should discuss the limited follow-up beyond five years. It is unknown whether moderate hypofractionation might have excess acute or late toxicity compared to conventional hypofractionation in, for example, elderly patients, those with larger gland volumes, or those with significant baseline voiding dysfunction.

3. Men should be counselled about the small increased risk of acute gastrointestinal (GI) toxicity with moderate hypofractionation. Moderately hypofractionated EBRT has a similar risk of acute and late genitourinary and late GI toxicity compared to conventionally fractionated EBRT. However, physicians should discuss the limited follow-up beyond five years for most existing randomised clinical trials (RCTs) evaluating moderate hypofractionation. The only applicable statistics given comparing conventionally and hypofractionated radiation were based on Aluwini et al., who found that grade ≥2 GI toxicity up to 120 days post-RT in the HYPRO trial was more common with hypofractionation (42 % versus 31 %, OR 1.6, 95 % Cl: 1.19–2.14). Grade ≥3 toxicity was uncommon (~6 %) and was similar between hypofractionated and conventional fractionation.

Consults with patients were structured normally, with an initial history and examination, followed by a discussion of their treatment choices. Treatment options potentially included active surveillance, surgery, EBRT, brachytherapy and androgen deprivation therapy (ADT). EBRT was to be delivered using our usual program of prostate-specific membrane antigen positron emission tomography (PSMA PET) staging of high risk patients, intensity-modulated radiation therapy (IMRT), fiducial marker insertion, spacer hydrogel insertion, MRI-CT fusion. During treatment we follow a bladder and bowel regime, with daily cone beam computed tomography (CBCT). Patients on treatment with a change in bowel anatomy in the high dose area were replanned.

When discussing treatment options, the initial discussion mentioned that there was a one month or two month option of IMRT which would be discussed in more depth should the patient be interested in pursuing radiation. At the initial or subsequent consultation, once the patient had decided they wished to have IMRT, an in depth discussion of the 20 vs 45 fraction options occurred. This discussion was facilitated using the decision aid (Fig. 1). If patients were unsure they were given the aid to take home, and a further appointment was made to obtain the decision.

In order to ensure the discussion was understood and the choice was valid, patients were asked why they had made their decision, with multiple reasons allowed. We also asked patients whether they were happy being involved in the process. If patients were unhappy, or wished the specialist to decide for them, the radiation oncologist decided on the fractionation schedule.

Univariate and multivariate analyses (using binomial logistic regression) of the effect of age, ECOG, cancer risk group, distance from the cancer centre, work/carer status, baseline GI and genitourinary (GU) symptoms, insurance status, driving status, and doctor facilitating the discussion on fractionation decision were undertaken using SPSS (IBM Corp. Version 21.0. Armonk, NV). This work was reviewed by the applicable HREC and was deemed to be a quality assurance activity.

### 3. Results

Between June and December 2018, 124 patients were seen with localised prostate cancer. All patients were offered hypofractionation (60 Gy in 20 fractions over 4 weeks) or conventional fractionation (81 Gy in 45 fractions over 9 weeks) with reference to the decision aid. Three patients were unable to come to a decision and all received the hypofractionated regime. Patient demographics of the remaining 121 patients are shown in Table 1. The median age was 72 (range 50–90), 49.6 % had intermediate risk disease, and 50.4 % high risk prostate cancer.

Overall, 33.9 % of patients chose the hypofractionated regime, with all patients receiving the fractionation schedule they chose. The proportion choosing hypofractionation fell to 23.5 % for patients under 75 years of age, 42.3 % for patients living within 50 km (30 miles) of the treatment centre, and 14.3 % for patients with baseline GI symptoms. The results are displayed in Table 2.

On multivariate analysis, age under 75, living within 50 km (30 miles) of the treatment centre, and having baseline GI symptoms significantly predicted for choosing conventional fractionation.
Based on several large studies, there are two options we offer for providing radiation for your prostate cancer.

We can treat your cancer with either 45 treatments, 5 days a week over 9 weeks,

OR with 20 treatments, 5 days a week over 4 weeks.

<table>
<thead>
<tr>
<th>45 treatments</th>
<th>20 treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>What is the same about these treatment options?</strong></td>
<td><strong>What is different about these treatment options?</strong></td>
</tr>
<tr>
<td>No matter which one you choose:</td>
<td><strong>45 treatments</strong></td>
</tr>
<tr>
<td>Your chance of being cured 5 years from now is the same.</td>
<td>Takes 2 months to complete.</td>
</tr>
<tr>
<td>Your chance of being alive 5 years from now is the same.</td>
<td>High chance of being cured 10-15 years from now.</td>
</tr>
<tr>
<td>The chance of side effects 5 years from now is the same.</td>
<td>High chance of being alive 10-15 years from now.</td>
</tr>
<tr>
<td>The cost to you is the same (there are no out of pocket expenses with radiation).</td>
<td>Lower chance of moderate bowel side effects during treatment. 31% chance, but these usually resolve within a month or two of finishing radiation.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>20 treatments</th>
<th><strong>What is uncertain about these treatment options?</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Your Choice</strong></td>
<td>We do not know whether the chance of cure is the same or different after 5 years.</td>
</tr>
<tr>
<td>You can decide about which treatment you want, if you wish. Please ask me any questions you wish. If you need time to think about it you may take this away and see me in a few days for another discussion. If you are not able to make up your mind, I can make the decision for you.</td>
<td>We do not know whether the chance of being alive is the same or different after 5 years.</td>
</tr>
<tr>
<td>If you have decided, what treatment do you wish to have? 45 / 20 / Cannot decide</td>
<td>We do not know whether the chance of having side effects is the same or different after 5 years.</td>
</tr>
<tr>
<td>So that I can make sure of your understanding, what is the reason for your decision?</td>
<td>How do you feel about being involved in the decision?</td>
</tr>
</tbody>
</table>

Fig. 1. Decision aid.

Insurance status, clinician seeing the patient, baseline genitourinary symptoms, work/carer status, ECOG, cancer risk group and driving status did not impact choice.

Reasons for choosing conventional fractionation were certainty of long term results (84 %) and lower acute bowel toxicity (51 %). Of the 80 patients who chose conventional fractionation, 35 chose it for long term results, nine due to increased risks of acute GI toxicity, 32 for both. Three patients chose conventional fraction for other reasons in addition to reasons relating to long term results and toxicity risks: one patient stated the referring urologist had told them radiation was for 45 fractions, one patient chose conventional fractionation because friends had been treated with 45 fractions with good outcomes, and one patient stated he was looking forward to his time having treatment and did not want this time curtailed. Three patients chose conventional fractionation only for other reasons: one was told radiation would take two months by the referring urologist, another was told by the referring urologist that conventional fractionation was better, and the third preferred
higher cost and being less convenient. It is thus evident that not all patients value convenience as their main priority, and that patients may differ from their treating physicians in terms of fractionation preference.

Since patients’ priorities may differ from what oncologists consider important, there is a need to ascertain the patients’ viewpoint. Decision aids may have a role here; their use generally improved patients’ knowledge and lowered decisional conflict across a range of medical treatments. In radiation oncology, these decision aids often focus on different types of treatments, with few aids specifically outlining different fractionation schedules. Anecdotally, in our centre, decisions about fractionation schedules are almost exclusively made by the radiation oncologists, with patient preferences (where choices are available) infrequently obtained.

With respect to prostate hypofractionation, the lack of patient involvement in decision-making appears to occur in multiple centres in Australia and New Zealand (based on personal communication from lead prostate cancer radiation oncologists in a number of Australian and New Zealand centres), with patients in some centres being treated almost exclusively with hypofractionation. This is despite awareness of the ASTRO statement, and full endorsement of the statement by the Faculty of Radiation Oncology Genitourinary Group (FROGG) of the Royal Australian and New Zealand College of Radiologists (RANZCR).

In our own cancer centres we sought to introduce prostate hypofractionation in an ethical manner, trying to provide patients with a balanced discussion based on the ASTRO consensus guidelines, incorporated into a shared decision-making process. To that end we believed a decision aid would be helpful and results of the present study support that view.

The wording of our decision aid was based on the ASTRO guideline, being a consensus statement based on a review of the literature by well-regarded experts, and endorsed by many international organisations. Our decision aid, in following the ASTRO Consensus guideline, states that despite equivalence at 5 years, we do not know whether cure, survival or side effect rates are the same or different after 5 years. It is possible that some clinicians will disagree, believing that there are no differences even beyond 5 years. Indeed, our own view is that there will likely be no difference. However, we worded the decision aid to avoid our own views, opting instead to follow the ASTRO guideline. In support of our interpretation, we note that the consensus guideline outlines that with hypofractionation “current evidence supports similar early cancer control”, but that “there are limited published outcomes beyond five years for moderate hypofractionation”, and that when discussing outcomes and toxicity that “physicians should discuss the limited follow-up beyond 5 years for most existing RCTs evaluating moderate hypofractionation”, and that “conventional fractionation ... is supported by longer-term results”. They also acknowledge that biochemical endpoints used in most studies are “imperfect surrogates for more important longer-term oncologic outcomes including disease-specific and overall survival”, and they go on to state that “additional follow-up will be valuable in establishing the impact of these moderate hypofractionation regimens on long-term cancer control”. It is clear to us that our wording is consistent with the ASTRO document.

Decision aids may incorporate logistics, differences in efficacy or toxicity, and sometimes costs. Uncertainty is not usually a key component. We included uncertainty as that, as mentioned, appeared to be an important caveat highlighted by the ASTRO Consensus statement. We were surprised to find that this would play such an important role in patient decision-making. In fact, the largest contributor to patients deciding against hypofractionation was the uncertainty with that approach in terms of long term
results. Patients specifically cited uncertainty of long term cure rates as well as toxicity. Patients were told that in the long term, hypofractionation was anticipated to be the same as conventional fractionation, however it may have better, worse, or equal long term cure rates and side effects. Consumers appear to have increasing health literacy,\textsuperscript{10} and from our experience it appears they place high value on long term certainty of results. This would appear to be particularly important for prostate cancer patients, where differences in efficacy and toxicity between regimens may not occur in the first few years. Given the results of our cohort it would appear that radiation oncologists must include uncertainty as an important part of any discussion with patients about their treatment. This would seem to be particularly important when introducing new techniques into practice. Radiation oncologists must also not assume that patients prioritise convenience above other factors.

Despite the small differences in acute toxicity associated with the two regimens (which patients were told resolves after treatment), 51 % of patients included toxicity in their decision, and for 11 % of patients it was the sole reason for choosing longer fractionation schedules. For some patients, any increased risk of toxicity, even temporary, was considered sufficient to offset the convenience of a shorter schedule. It would be extremely interesting to see how small differences in long term toxicity could impact on patient decision-making, if those differences ever eventuated.

Several patients made a fractionation decision for reasons outside of the decision aid. Some patients chose conventional fractionation because friends had experienced it, or referring doctors had recommended it. One patient chose hypofractionation because he wanted to be a guinea pig (i.e. the subject of research), even though this was not a research project. As hypofractionation becomes more established in the minds of referring doctors and the community, it is possible that more patients will choose hypofractionation in the years to come.

Distance was stated as an important factor by many patients, and was a significant factor influencing fractionation choice on multivariate analysis. Our rural centres cover a population living within a 20,000 square km area (nearly 8000 square miles), with many patients travelling each day or staying in on-site accommodation during treatment. Local patients within 50 km (30 miles) of our units, preferred conventional fractionation 75.7 % of the time. The critical impact of distance was highlighted by one patient who initially chose hypofractionation as he lived over 100 km from the centre. Subsequently this patient’s brother moved close to the centre. The patient, now having a place to stay close by, changed his mind and wanted conventional fractionation. He stated that he always had concerns about toxicity and uncertainty, but distance was the over-riding factor initially. We would expect the patients living in metropolitan centres to be even more likely to choose conventional fractionation, given the proximity of centres to the population. Further research could evaluate the decision-making of patients living in metropolitan areas.

Age was important in decision-making for some patients, and was significantly associated with fraction choice in our cohort. Several elderly patients said they were happy with hypofractionation because they only expected to live a little longer than 5 years, so longer term results were not important. Other factors that we thought may play a role included baseline urinary and bowel function, private insurance status (a surrogate for socioeconomic status), risk group (and how worried patients were about their cancer), and whether the patient drove or worked (or was a carer). Of these, only the existence of baseline GI symptoms was significantly associated with patient choice, with only 14.3 \% of patients with baseline symptoms choosing hypofractionation. As one patient put it, “There is no way I want my bowel problems to be worse”, and he wished to do everything feasible to reduce the risks.

The decision aid itself was well received, with all patients happy being involved in using it to select preferences. This was true even for the three patients who could not make up their mind about treatment. The aid itself was useful for patients to take away and think about. Many patients could not make an initial decision, but came to a decision in the weeks following the initial consultation, after reviewing the aid at home. Several patients made an initial decision for hypofractionation at first consultation, but changed their mind after reviewing the aid at home. One patient also did the opposite, changing his choice from conventional to hypofractionation after review of the aid at home. This highlights the importance of patients not being forced to make treatment decisions at the initial consultation.

A possible limitation of our evaluation is that in our practice, there is no cost differential for patients between the two options. It is possible that in some practices there is a difference, which would need to be incorporated into the decision-making process for these patients. In our previous study from Singapore, fractionated radiation had increased costs; however, that affected decision-making in relatively few patients.\textsuperscript{6} Another limitation is that in our decision aid and subsequent discussion we made no reference to the departmental and governmental resource advantages for hypofractionation. This is not part of treatment discussions with any patient in our practice, and it is uncertain how this might influence patient choice.

A limitation of the decision aid is that it was not beta tested. The aid was designed after consultation with a number of radiation oncologists and several patients who had previously undergone radiation therapy. It was based on previous aids designed by the authors to facilitate fractionation choice. Although the aid itself, designed for daily use, was not beta tested, we note that its validity is at least partially confirmed through its use. Validity is supported by the fact that patients indicated understanding of the phrases, noting that discussion occurred around the decision aid as part of a normal clinical discussion with the usual clarification of patient understanding that occurs in consultations. Validity is further supported by the fact that only 3 patients were unable to decide based on the aid, and that patients chose their fractionation schedule for reasons consistent with information contained within it. Only four patients made a choice solely for reasons not listed in the aid (noting that most of these reasons did not relate to invalid information within the aid itself).

One potential criticism is that we might be biased, either through the design of the decision aid or in the discussion surrounding its use in practice. Clinician bias may occur for example due to personal experience of what works well, resistance to change, wish to free up machine time to avoid waiting lists, or for financial reasons. In our department, over the timeframe being evaluated, it would be impossible to discern whether bias occurred, the magnitude of it, or its direction and impact on patient choice. In a department such as ours often experiencing extended waiting times for cancer patients (3–4 months for prostate patients over the period in question), we have a general bias towards hypofractionating patients. For this reason, we have some of the highest hypofractionation rates in our state for breast cancer,\textsuperscript{17} hypofractionating almost all patients with conserved breast cancer / DCIS and post-mastectomy, including patients having nodal irradiation. Patients are hypofractionated regardless of age, comorbidity or breast reconstruction. We also have some of the highest rates of hypofractionation for bone pain palliation.\textsuperscript{17}

Potential bias due to financial remuneration is a particularly interesting area. It is uncertain whether longer fractionation schedules for prostate cancer patients would result in a financial benefit for clinicians or the department. In our practice, not infrequently patients are sent to other departments for radiation therapy due to our wait lists. This is a financial loss to the department and some
treating specialists. Since simulation and planning is reimbursed much more than treatment fractions, financially it may be more rewarding to treat a greater number of patients in our departments by hypofractionating them, rather than lose some patients to other departments. We have not done any modelling for this and it is outside the scope of this paper, however it is an area that deserves further investigation.

The uncertainty of financial benefits or detriments notwithstanding, of the nine clinicians involved in administering the decision aid, eight were fully salaried by the state government, and receive no financial benefit from patient treatment. None of those eight are privy to financial budgets, nor have any financially related or patient volume related performance indicators related to their employment. There would be no financial bias for these eight clinicians. The remaining contracted clinician does receive a financial benefit from patients treated. It is this radiation oncologist that wished to introduce hypofractionation into the centres. It could be argued that if the clinician in question was financially driven there would be no reason to introduce hypofractionation. This particular radiation oncologist also treats breast cancer, and is one of the highest breast cancer hypofractionaters in our state.17 This hypofractionation advocacy seems counter to any financial desire to avoid prostate hypofractionation. Further support of the lack of financial motivation was the fact that there was no significant difference in patient choice of hypofractionation schedule between clinicians. Finally, we note that all patients who were unable to make a choice using the decision aid were hypofractionated by the treating radiation oncologist.

Of course, we cannot completely exclude the possibility that some type of bias occurred in consultations, nor whether bias was towards hypofractionation or conventional fractionation. We are unaware of any decision aid study that has excluded bias, and bias is therefore a generic limitation of decision aid studies. These same forms of bias may exist in any doctor-patient interaction, with or without use of an aid. Our aim was to provide information within our decision aid in as unbiased a manner as possible, presenting information directly from the ASTRO guideline. If clinicians disagree with statements used by ASTRO, such as “physicians should discuss the limited follow-up beyond five years for most existing RCTs evaluating moderate hypofractionation”, “Men should be counseled about the small increased risk of acute gastrointestinal (GI) toxicity with moderate hypofractionation”, or “conventional fractionation...is supported by longer-term results”, then we suggest lobbying the guideline authors for changes in future updates. Our intention is to update the decision aid once future updates to the ASTRO guidelines are published, and a comparison of these results will be fascinating.

Further research could look at patient satisfaction and decision regret surrounding patient choice, although in our experience these are extremely high with conventional fractionation, with only 0.5% of patients unlikely to choose dose-escalated IMRT again.18 Thus any differences based on fractionation schedules received may not be readily apparent.

An area of interest would to be compare different conventionally fractionated and hypofractionated schedules. Our practice wished to introduce hypofractionation as an alternative to our current conventional fractionation schedule of 81 Gy in 45Fx. This schedule has excellent long term results both in our practice (via our long term quality monitoring program), and in published evaluations.19 The ASTRO consensus guideline provides overarching guidance for the use of hypofractionation, and our two schedules of 81 Gy in 45 fractions and 60 Gy in 20 fractions are both consistent with the guideline statements. It would be interesting to see how patients would view a comparison of, say, 78 Gy in 39 fractions with the 20 fraction schedule. The smaller time saving with the latter comparison may result in even fewer patients choosing hypofractionation.

Another area of interest would be to design different decision aids based on specific studies, rather than a consensus guideline. For example, the ASTRO consensus guideline states that there is a small increase in acute GI toxicity with moderate hypofractionation compared to conventional fractionation. This difference is summarised as a generic difference applicable to all hypofractionation schedules. Some may argue that results of specific studies show differing toxicity results, however our purpose was to design the aid based on the generalised ASTRO consensus guideline rather than picking individual studies. We thought that this would reduce bias. It would be interesting to see how different decision aids based on individual studies might affect patient choice.

Finally, not all clinicians will necessarily agree with the wording of our decision aid. We are equally certain that in the absence of a decision aid, not all clinicians would agree with each other’s approach to discussing these issues with patients. As far as we are aware, this decision aid is the only one in use in our state, and we have been unable to identify any other published decision aids for fractionation choice in localised prostate cancer. We would be very interested to see evaluations of different aids, with different wording, in different patient cohorts, and this is an area ripe for investigation.

5. Conclusions

Departments implementing prostate cancer hypofractionation should incorporate patient choice in the decision regarding fractionation. In our experience most patients prefer conventionally fractionated radiation, and we believe those preferences should be respected. The use of a decision aid may help patients make an informed choice.

Financial disclosure

None declared.

Conflict of interest

None declared.

References


