Abstract

Introduction: Randomised trials show equivalent rates of survival, local control and late toxicity with hypofractionationed breast radiotherapy (HBRT) and standard fractionation (SBRT). Reviewing patients’ preferences given evolving evidence and patients’ other considerations would inform our understanding of determinants in treatment choice. It would also guide the planning of radiotherapy resource usage. This study’s aim was to determine patients’ choice of schedule and reasons.

Methods: Using a decision board, advantages and disadvantages of adjuvant radiotherapy with 42.56 Gray in 16 fractions, and 50 Gray in 25 fractions were discussed with patients with T1-T2 N0 M0 breast cancer. Patients were asked to choose a fractionation schedule and provide their reasons. This was correlated with patient demographics.

Results: 74 patients were recruited of which 48.7% chose HBRT. Patients 50-60 years were 5.42 times (95% CI 1.72 to 17.02, p=0.004) and patients 60-70 yrs were 10.59 times (95% CI 2.4 to 46.75, p=0.002) more likely to choose HBRT than patients less than 50 yrs. HBRT was chosen for increased convenience (97%) and lower cost (42%) whilst SBRT for the reason of longer follow up (97%).

Conclusion: Older patients chose HBRT for the advantage of cost and convenience, while younger patients chose SBRT because of longer length of clinical experience and follow-up. Research into patient preferences for breast radiotherapy would inform management of patient care and inform healthcare policy and resource allocation.

Keywords: Breast neoplasms; Decision making; Shared; Dose fractionation; Patient preference; Radiotherapy; Adjuvant

Abbreviations: HBRT: Hypofractionationed Breast Radio-Therapy; SBRT: Standard fractionation Breast Radio-Therapy; ECOG: Eastern Cooperative Oncology Group

Introduction

Early stage breast cancer treated with breast conservation surgery presents a unique situation where various options for adjuvant radiotherapy regimens exist and are well-studied with competing outcomes in efficacy and toxicity. A plethora of data is available and more will be contributed to the literature. Existing data is open to interpretation and physicians and national health policy disagree on the optimal choice of treatment. Furthermore, the patient population considering this treatment traverses the spectrum of ages and has competing considerations apart from the medical data [1-5]. The discussion with the patient on the choice of treatment is necessarily nuanced as is the patient’s decision-making process.

Since the conduct of this study, publications presenting data on the experience of acute toxicities of adjuvant breast radiation therapy suggest hypo fractionation to have improved outcomes [6,7]. Only two randomized trials have published long-term follow-up data demonstrating equivalence in local control and late effects (long term cosmesis) for hypo fractionated adjuvant radiation therapy for early stage breast cancer [8,9].

While patients were recruited for this study (from November 2009 to March 2010), other than results from Whelan et al. [8], the other randomized trials had only a median follow up approximating 5 years. Despite the relatively short follow up period in a disease with a long natural history, the medical...
community has been accepting of the use of HBRT. Its use is advocated in many national guidelines with the clinical consideration that any potential benefit from the longer schedules with higher total dose may be offset by the lower cost and increased convenience for patients who chose HBRT. Since the time of this study, the publication of updated START B [9] data suggests hypo fractionated regimens with lower doses may have improved late cosmetic outcomes and equivalent survival compared with standard fractionation RT.

A patient’s ultimate choice of therapy would be contributed to by a myriad of factors including:

a) Data to date establishing equivalent outcomes for survival over durations studied,

b) START B data demonstrating a possible benefit for cosmesis with HBRT,

c) physician interpretation of emerging data for efficacy, toxicity outcomes from studies of adjuvant radiotherapy in breast cancer as well as toxicity data from studies of other tumour sites that share the same organs at risk,

d) how information is summarized and conveyed to the patient in the setting of a consult,

e) physician’s professional experience, preferences and biases,

f) non-medical factors considered by the patient such as convenience, personal values, and perception of acceptable risk

g) pertinent remuneration and health economics policies

Certain technical and treatment-related factors such as breast size, would also factor into whether a particular patient would be offered a specific radiation therapy regimen. Larger breast size would give rise to prohibitively greater dose in homogeneity which may render hypo fractionated regimens impracticable due to the principle of ‘double trouble’ and its effect on late toxicities. Looking forward, where there is 15 year data for SBRT outcomes [10], longer term data from hypo fractionation trials is awaited.

Given all of these reasons, it is not surprising that differences in fractionation preferences between centres have been well documented [11-13]. When presented with a choice, patients may wish to have longer fractionations even with only a small potential benefit [14,15]. Studies have also demonstrated that a difference exists between what oncologists consider important and patients’ beliefs, as well as physicians’ understanding and perception of patients’ beliefs [16,17]. Patients have also indicated a wish to have more information about their disease and a desire for shared decision [18-20]. This is particularly true for patients with breast cancer.

Given the multiple uncertainties in predicting a patient’s final decision for adjuvant breast radiation therapy, we proposed using a decision board instrument based on the results of the Canadian breast cancer study to determine which fractionation schedule patients would choose [21]. Prior studies using decision boards have demonstrated that they are feasible and acceptable to both patients and doctors, resulting in improved communication and facilitating shared decision making [21,22]. Decision boards have been shown to be well understood and easily implemented in non-English speaking populations as well [23].

Methods

The primary end point of this study was to determine what percentage of patients of our urban practice diagnosed with T1 - T2 N0 M0 breast cancer, following breast conservation surgery would choose HBRT over SBRT. Secondary end points were to elucidate the patient variables that influence this decision. In order to investigate these questions, a decision board based on the results from the keynote study by Whelan et al, was used (Table 1) [8]. The board presented a summary of the similarities and differences of two options of adjuvant breast radiotherapy regimens: 50 Gray in 25 fractions and 42.56 Gray in 16 fractions in terms of local control, cosmetic outcome, late toxicity and length of follow up. Factors such as cost and number of visits were also shown.

Decision Board Used To Counsel Patients on Hypo- fractionation

Table 1: The differences and similarities between the 2 treatments.

| Choices | 16 Treatments (42.5 Gy/ 16Fx) | 25 Treatments (50 Gy/ 25Fx) |
|---------|-------------------------------|-----------------------------|
| Similarities i.e. 95% confident that there is no statistical difference between the arms | | |
| Risk for re-growth of the tumour in the breast at 10 years | 6.2% | 6.7% |
| Good/Excellent Cosmetic Outcome at 10 years | 70% | 71% |
| Moderate/Severe late radiation side effects to the skin at 10 years | 6% | 3% |
| Moderate/Severe late radiation side effects to the tissue below the skin surface at 10 years | 8% | 4% |

Differences
Based on one large previous medical study, there are two options for giving radiotherapy (RT) to your breast. We can treat with either 16 treatments (Fx) or 25 treatments (Fx). The treatments both have the same chance of controlling the disease in your breast – overall about 93% at 10 years from diagnosis. There is no difference in survival or quality of life between the treatments. However, as the median follow up for the study is only 12 years, we cannot be certain that the results of the 2 treatments will remain similar beyond the first 12 years (Table 1).

Prior to commencement of this study, a pilot study of 10 healthy women volunteers (aged between 24-69 years old) was done to confirm instrument validity and reproducibility. Our pilot study found that 50% of patients chose HBRT. Thus the sample size was determined on a point estimate of 50% choosing HBRT, with 95% confidence interval from 40% to 60%. A total of 74 patients were required.

The study protocol was reviewed and received institutional ethics board approval. The study population was drawn from patients consulted by radiation oncologists at the National University Cancer Institute, Singapore. Eligibility criteria was similar to that used in the trial by Whelan et al. [8], i.e. women with staged T1 or T2 primaries, node negative adenocarcinoma of the breast treated with lumpectomy and either sentinel lymph node biopsy or axillary clearance, maximum width of breast tissue <25cm and capacity to provide informed consent and take part in the process of shared decision making.

All potentially eligible patients were identified by participating radiation oncologists at the time of first consultation for radiotherapy. Using the decision board instrument as a visual aid, consenting eligible patients were counselled regarding the comparative risks and benefits of SBRT and HBRT. Patients and any accompanying family were allowed time to ask questions and clarify information. The choice of adjuvant radiotherapy fractionation was made either at that visit or confirmed at the time of radiotherapy simulation. After the decision was made, patients were asked without prompting, reasons behind their decisions. According to their decision, patients then received either whole breast irradiation of 42.5 Grays in 16 fractions over 22 days or whole breast irradiation 50 Grays in 25 fractions over 35 days. A boost to the tumour bed of 10 Grays in 5 fractions was used for all patients.

### Statistical Analysis

The main outcome measure was choice of HBRT, and we used the binary logistic regression model to look at the association with the following factors: patient age, sex, race, education level, distance from home to hospital, travel time to hospital, mode of transport to hospital, paying class, employment status, social support, whether decision was made by the patient or family, stage of disease and performance status as scored by the Eastern Cooperative Oncology Group (ECOG).

Data analysis was performed using Stata V10.2 (Stata Corp, College Station, TX, USA), with level of significance set at 5%.

### Results

Patients were recruited over a 4 month period from November 2009 to March 2010. 74 consecutive patients with node negative stage I or II breast cancer were eligible and entered onto the study. None of the identified eligible patients refused participation in the study. The median age of consenting patients was 54 years old (range 36 to 72 years). 85.1% were Chinese, 5.4% were Malay and 6.7% were Indian. 77% of patients had high school education or greater and 45.9% were employed outside the home. 67.6% of patients received government subsidy for their treatment. 17.6% lived alone, 66.2% with spouse only and 16.2% with children. 78% of patients made the decision for which fractionation they wished to undergo on their own. Median distance from the patient’s home to hospital was 9km (range, 2 to 23km), median travel time was 20 min (range 5 to 60 min) and 58% of patients used public transportation to reach the hospital.

Patient choice of fractionation schedule by characteristic is presented in Table 2. Of the 74 patients (48.7%) chose the schedule of 42.5Gy in 16 fractions (95% confidence interval, 36.9% to 60.6%). On univariate analysis, the only patient factor that predicted for patient’s choice was increasing age (OR 1.09, 95% CI 1.03 to 1.15, p=0.002). Patients aged 50 years to 60 years were 5.42 times (95% CI 1.72 to 17.02, p=0.004) and patients 60-70 years were 10.59 times (95% CI 2.4 to 46.75, p=0.002) more likely to choose the 25 fractions treatment.

| 1. | Median reported clinical follow up | 12 years | >20 years |
|----|----------------------------------|----------|----------|
| 2. | Estimated cost to patient in Singapore dollars |          |          |
|    | Government subsidized total cost  | $2321    | $2849    |
|    | Private Singaporean total cost   | $6392    | $7898    |

| 3. | Number of visits including radiotherapy planning visit | 17 | 26 |

### Reasons for your decision

|          |
|----------|
| Lower cost |
| More Convenient |
| Longer median follow up |

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likely to choose HBRT than patients less than 50 yrs. Patient decision-making was not analyzed to be significantly affected by any other patient factor (p >0.1 for all other variables). Patient decision-making was also not influenced by which radiation oncologist they consulted with (Table 2).

Table 2: Patient choice of fractionation schedule by characteristic.

| Characteristic                          | Number Choosing Hypofractionation | Number Choosing Standard Fractation | Percentage Choosing Hypofractionation (%) |
|----------------------------------------|-----------------------------------|-------------------------------------|----------------------------------------|
| Age (years)                            |                                   |                                     |                                        |
| <50                                    | 9                                 | 26                                  | 25.7*                                  |
| 50-60                                  | 16                                | 7                                   | 69.6*                                  |
| >60                                    | 11                                | 5                                   | 68.8*                                  |
| Race                                   |                                   |                                     |                                        |
| Chinese                                | 29                                | 34                                  | 46.0                                   |
| Malay                                  | 4                                 | 2                                   | 66.7                                   |
| Indian                                 | 3                                 | 2                                   | 60.0                                   |
| Education level                       |                                   |                                     |                                        |
| Did not complete high school           | 11                                | 7                                   | 61.1                                   |
| High school diploma and above          | 25                                | 31                                  | 44.6                                   |
| Employment status                     |                                   |                                     |                                        |
| Unemployed/ Retired                    | 19                                | 21                                  | 47.5                                   |
| Part time/ Full time                  | 17                                | 17                                  | 50.0                                   |
| Cost                                   |                                   |                                     |                                        |
| Government subsidized                  | 27                                | 23                                  | 54.0                                   |
| Private                                | 9                                 | 15                                  | 37.5                                   |
| Social Support                         |                                   |                                     |                                        |
| Stays alone                            | 6                                 | 7                                   | 46.2                                   |
| With spouse only                       | 22                                | 27                                  | 44.8                                   |
| With extended family                   | 8                                 | 4                                   | 66.7                                   |
| Decision made by                       |                                   |                                     |                                        |
| Patient alone                          | 29                                | 29                                  | 50.0                                   |
| Jointly with family                    | 7                                 | 9                                   | 43.7                                   |
| Distance from home/work place to hospital (km) |   |   |                                        |
| 2-9                                    | 18                                | 24                                  | 42.9                                   |
| 9-23                                   | 18                                | 14                                  | 56.2                                   |
| Travel time to hospital (min)          |                                   |                                     |                                        |
| <20                                    | 18                                | 22                                  | 45.0                                   |
| 20-40                                  | 11                                | 8                                   | 57.9                                   |
| 41-60                                  | 7                                 | 8                                   | 46.7                                   |
| Mode of transport                      |                                   |                                     |                                        |
| Public transport                       | 18                                | 20                                  | 47.4                                   |

Patients who chose HBRT did so for reasons of lower cost alone in 3.0%, increased convenience alone in 58.3%, and both lower cost and increased convenience in 38.9%. The patients who chose SBRT cited factors that shaped their decision to be those of more clinical experience with its use and the longer length of follow-up available.

Discussion

Our study is the first to directly explore the question: "If the medical community assesses clinical equivalence between HBRT and SBRT in terms of toxicity, local control and survival, when presented with the choice what would patients choose based on other end points such as cost, convenience and clinical experience?" The main findings in the current study were two-fold: First, that the majority of women with breast cancer preferred to be involved in the decision making process of radiotherapy regimen for their breast cancer; Second, that patient’s perspective of risk differs from that of the physician on their behalf as shown by the difference in the age group of patients who were willing to accept HBRT over SBRT. Older
patients tended to choose HBRT, while younger patients were concerned about relative demonstrated duration of efficacy and preferred SBRT.

While older patients (OR 5.42 for patients 50-60 years of age and OR 10.59 for patients 60-70 years, compared to patients <50 years of age) were more likely to choose HBRT for reasons of cost and convenience, younger patients (less than 50 years of age) placed greater weight on the length of clinical experience and follow up available. This difference in belief was reflected in the significantly higher number of women less than 50 years of age choosing SBRT over HBRT (p=0.002) in spite of the considerable difference in financial cost borne by the patient between the two fractionation regimens (up to $1506 Singapore dollars, approximately $1000 US dollars) and added inconvenience of SBRT.

Adjuvant radiotherapy for early stage breast cancer is unique in various ways:

i. the heterogeneous patient group it serves. Patients in this group span a spectrum in terms of age, social commitments, and opinions on importance of factors such as survival, cosmesis and convenience.

ii. in the relative diversity of treatment regimens available with comparable outcomes. Treatment regimens that have been substantiated by long term evidence with 10 to 15 year follow-up exist for various courses of HBRT and SBRT. Recent evidence suggests HBRT may have a superior acute toxicity profile [6,7]. However the natural history of early stage breast cancer preferably would have duration of follow-up of more than 10 years for sufficient assessment of its efficacy.

iii. the share of a given Radiation Oncology department’s clinical service that it occupies.

Length of follow up may still be of concern to patients, though medical opinion may generally interpret the existing published data to show both options equivalent by local control and survival. ASTRO guidelines from 2011 also highlight concerns with hypo fractionation in adjuvant breast irradiation as the single standard [24]. Despite promising START B data, concerns on the adoption of hypo fractionation in adjuvant breast irradiation include:

a) small representation of patients with regional lymphatic irradiation, hence generalizability of safety data from START trial to such patients
b) The risk of brachial plexus morbidity though likely low is unknown. Cardiac late toxicity in hypo fractionation compared with standard fractionation is also a concern.
c) An exclusion criterion of the START trials was immediate breast reconstruction. As immediate reconstruction is common practice in some populations including this study’s, the use of START toxicity data may not apply here

These results serve as a useful reminder of the nuances of physician interpretation of current evidence. Furthermore, in this study, a script was not drafted for the consult- use of which would have been impractical- so presentation of the efficacy and toxicity profile of treatments would have understandably varied from consult to consult. While these results indicate the considerations important to patients when making a decision on adjuvant breast radiation therapy, it is noted that our trial was confined to a single institution with its unique parameters for value-driven healthcare. Singapore is a highly urbanized city state. No patient in our sample needed to travel more than 60 minutes for her daily treatment. In addition, the cost structure of radiotherapy as defined in our study may not be applicable to other countries. Our sample size consisted only of Asian patients whose views on treatment risk and whose weight age placed on different patient and treatment factors may be different from Western counterparts.

The decision board presented medical factors (survival and local control outcomes, late toxicities, duration of follow-up) generalizable across populations with different geographic and socioeconomic characteristics. But it also contained information that is unique to each patient population, in this case, convenience (in numbers of visits) and financial cost. An interesting area for future research would be to determine if convenience and cost, variables that would change in a different population setting, would be considered important enough for patients to decide differently, given the same medical information.

Patient preference between either adjuvant breast radiotherapy regimen is dependent on many factors, the importance of each being weighted differently according to the individual. Furthermore, aggregate preferences across populations with different cultural and social backgrounds would differ as well. Our study summarizes how these factors are considered and affect patients in a specific urban population in the context of the cost structure unique to Singapore during the period of the study’s conduct. Future studies with a more diverse population from a broader geographic region, would provide a more rounded understanding of the impact of social factors and patients’ opinion on medical outcomes, on decision-making, and may improve the generalizability of the results of this study. As breast radiotherapy comprises a large share of the workload for many centres especially in developed countries, such results will help in resource allocation and workforce projections.

The results of our study illustrate the importance of considering individual patient preferences during the treatment decision making process. Thus it is clear that research into patient preferences for breast radiotherapy would inform organization of radiotherapy and inform healthcare policy and resource allocation. Our results offer insight into the discrepancy between medical opinion and patients’ actual preference, and while informative and locally applicable, individual centres would benefit from local, centre-specific data to guide planning.
at the level of an institution’s Radiation Oncology unit and that of national healthcare planning.

Conclusion

Older patients chose HBRT for the advantage of cost and convenience, while younger patients chose SBRT because of longer length of clinical experience and follow-up. Research into patient preferences for breast radiotherapy would inform management of patient care and inform healthcare policy and resource allocation.

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