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Original Article

Quality of Life in Male Breast Cancer: Prospective Study of the International Male Breast Cancer Program (EORTC10085/TBCRC029/BIG2-07/NABCG)

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Abstract

Introduction: Prospective data about quality of life (QoL) in men with breast cancer (BC) are lacking. A prospective registry (EORTC10085) of men with all BC stages, including a QoL correlative study, was performed as part of the International Male Breast Cancer Program.

Methods: Questionnaires at BC diagnosis included the EORTC QLQ-C30 and BR23 (BC specific module), adapted for men. High functioning and global health/QoL scores indicate high functioning levels/high QoL; high symptom-focused measures scores indicate high symptoms/problems levels. EORTC reference data for healthy men and women with BC were used for comparisons.

Results: Of 422 men consenting to participate, 363 were evaluable. Median age was 67 years, and median time between diagnosis and survey was 1.1 months. A total of 114 men (45%) had node-positive early disease, and 28 (8%) had advanced disease. Baseline mean global health status score was 73 (SD: 21), better than in female BC reference data (62, SD: 25). Common symptoms in male BC were fatigue (22, SD: 24), insomnia (21, SD: 28), and pain (16, SD: 23), for which women's mean scores indicated more burdensome symptoms at 33 (SD: 26), 30 (SD: 32), and 29 (SD: 29). Men's mean sexual activity score was 31 (SD: 26), with less sexual activity in older patients or advanced disease.

Conclusions: QoL and symptom burden in male BC patients appears no worse (and possibly better) than that in female patients. Future analyses on impact of treatment on symptoms and QoL over time, may support tailoring of male BC management.

Key words: male breast cancer; quality of life; prospective study; symptom assessment.

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Implications for Practice

In this prospective male breast cancer (BC) registry, baseline quality of life (QoL) and symptom burden in male patients with BC appears no worse (and possibly better) than that in female patients. Future analyses of later surveys from this study will assess the impact of specific treatments on changes in symptoms and QoL over time. These data will be useful in efforts to tailor treatments and target interventions for male BC.

Introduction

Male breast cancer (BC) is a rare disease that accounts for less than 1% of all cancers in men and about 1% of all BC.[1] Due to the rarity of the disease and the common exclusion of men from BC studies,[2] male BC-focused basic and clinical research is limited. Although recently a male BC specific subset analysis of a randomized phase III trial was reported,[3] most available data come from observational retrospective studies.[4-6] To improve our understanding of male BC biology and to optimize clinical management, a global collaborative effort, the *International Male Breast Cancer Program,* was launched in 2006. This program published the largest retrospective series to date of male BC patients with centrally reviewed clinical data and tumor samples[7]; this identified changes over time in male BC treatments, mirroring those in female BC.[8] Subsequently, the International Male Breast Cancer Program launched a prospective registry of newly diagnosed patients with male BC with clinical data and tumor samples (EORTC10085/TBCRC029/BIG2-07/NABCG). Enrolling from 2013 to 2017 in 7 European and 3 South American countries, and in the United States (Supplementary Table S1), this study aimed to gather information about modern tumor biology and treatments, and it included a correlative substudy to assess quality of life (QoL) and symptom burden, which have been woefully understudied in male BC.

Limited retrospective data are available regarding symptoms and QoL in men with breast cancer. In a Behavioral Risk Factor Surveillance System telephone survey comparing 198 men without cancer and 66 men with a history of BC who were diagnosed on average 12 years ago, poorer physical, and mental health was identified in BC survivors. Obesity, diabetes, and activity limitations due to a physical, mental, or emotional problems were also more common after BC.[9] Endocrine therapy side effects and persistence rates have been evaluated in several small studies,[10-13] but while male BC patients clearly have specific unmet needs for information in this setting,[14] QoL and physical and emotional symptoms near the time of diagnosis are still understudied. In one study of 78 men undergoing an evaluation for a breast abnormality in the United Kingdom, approximately 30% reported feeling embarrassed to see their doctor, and one fourth reported anxiety related to their diagnosis.[15]

We designed the QoL substudy to address gaps in knowledge regarding QoL and symptom burden around the time of diagnosis of male BC and over time thereafter to inform optimal treatment and survivorship care. Here we report the results of the baseline questionnaires of men who participated in the QoL substudy.

Patients and Methods

Study Design

Men with histologically proven breast cancer, age ≥18 years, newly presenting at a participating center or within 3 months prior to center activation (irrespective of the stage of disease, initial diagnosis date, or treatment received), and enrolling in the prospective registry of the International Male Breast Cancer Program (EORTC10085/TBCRC029/BIG2-07/NABCG) were eligible for the QoL substudy. Written informed consent was required: either one general consent for both parent and QoL study (in the Netherlands) or separate consents for both parent and QoL study for other participating countries (Switzerland, Greece, Ireland, Portugal, Serbia, Sweden, United States, Brazil, Mexico, and Peru).

Questionnaires

QoL was measured using European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30 version 3) and items from EORTC QLQ-BR23 and EORTC-PR25.[16] The EORTC QLQ-C30 is a well-validated 30-item scale that measures the primary dimensions of QoL, as well as specific cancer-related symptoms. It is composed of a global health/QoL scale, functioning scales (physical, role, emotional, cognitive, and social functioning scale), and symptoms scales/items (fatigue, nausea and emesis, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). The Breast Cancer Modular Supplement (EORTC QLQ-BR23) is a validated 23-item breast cancer-specific questionnaire that should be added to the EORTC QLQ-C30 to obtain additional information about QoL and symptoms that are prevalent in BC patients. It contains 5 multi-item scales to assess body image, sexual functioning, systemic therapy side effects, arm symptoms, and breast symptoms, as well as single items to assess sexual enjoyment, future perspective, and upset by hair loss. The multi-item scales and single items are divided into 2 groups: functional (body image, sexual functioning, sexual enjoyment, and future perspective) and symptom-focused (systemic therapy side effects, breast symptoms, arm symptoms, and upset by hair loss). In consultation with the EORTC headquarters QoL department, 4 of the BR23 items that are only appropriate for women (regarding physical attraction, feeling less feminine, difficulty looking at yourself naked, and dissatisfaction with your body) were omitted, gendered language in the instructions was edited to be appropriate for men, and 11 additional items from the PR25 (a 25-item modular supplement developed and validated for prostate cancer patients) were used to assess function (sexual activity and sexual functioning) and hormonal treatment-related symptoms (see Supplementary Fig. S1 for complete instrument administered). Scores for all scales and single items range from 0 to 100. High scores for functioning and global health/QoL measures indicate high/healthy levels of functioning/high QoL, whereas high scores for symptom-focused measures indicate a high level of symptoms/problems.

Statistical Analysis

Questionnaire forms were analyzed centrally by the EORTC statistics department. Descriptive analysis was conducted in patients with baseline QoL forms completed within 30

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days of date of registration to capture baseline status accurately. As information related to the course of QoL in time is not yet available, the clinical meaning of the QoL data was assessed by comparing[17] it to a normative (reference) population of men in 6 European general population studies,[18] and a population of 2782 women with all stages of BC (all stages) used for EORTC QLQ-C30 reference values.[19] Scores were reflected as mean (SD), or median (interquartile range, IQR).

Results

Study Enrollment

Between October 24, 2013 and March 01, 2017, a total of 557 patients were enrolled in the international prospective registry, the parent study (see Fig. 1), 445 of which at 46 sites participated in the QoL substudy. Consent forms were received from 422/445 men (95%) for the QoL substudy. The clinical database was locked on November 02, 2017 for this analysis. Baseline survey compliance was 95% (399/422), and 363/399 (91%) of patients completed that survey within 30 days of registration, making them eligible for analysis. Median age was 67 years (range 33-92). There were 114 respondents (45%) with node-positive early disease (M0) and 28 respondents (8%) with advanced disease (M1). Patient- and treatment characteristics are shown in Table 1. Median time from diagnosis to baseline survey was 1.1 months (range –0.8 to 206.0). Of 363 evaluable men, 193 (53.2%) men received at least one treatment modality prior to baseline QoL completion: 180 (49.6%) had received surgery, 24 (7%) had received radiotherapy, and 70 (19.3%) had started on systemic therapy (median interval with surgery 43 days, Q1–Q3: 24.5-89; 118 days with radiotherapy, Q1-Q3: 36.5-744; 43 days with systemic therapy, Q1-Q3: 13-121; see Supplementary Fig. S2 for combinations of therapies). The majority of patients were from Europe (75%), followed by the United States (21%) and South America (4%). More detailed inclusion data by country are shown in Supplementary Table S1.

EORTC QLQ-C30 Scores

QoL and symptom scores at baseline in the overall population are shown in Table 2. Mean global health status score was 73 (SD: 21) and mean social functioning score was 85 (SD: 22). Men's most commonly reported symptoms included fatigue (mean score 22, SD: 24), insomnia (mean score 21, SD: 28), and pain (mean score 16, SD: 23). With regard to items from the PR25 questionnaire, mean sexual activity score was 31 (SD: 26), and in those who were sexually active, mean sexual function score was 80 (SD: 18). Only 4 men were 40 or younger; they reported more fatigue, nausea/vomiting, pain, appetite loss, constipation, and financial problems than older men. There were no substantial differences in QoL or symptom burden between those with advanced stage and those with early-stage disease. In patients who were sexually active, sexual functioning tended to be worse in those with advanced disease, with mean score 68 (SD: 22) versus 81 (SD: 17) for those with early-stage disease. The effects of age and disease stage are shown in greater detail in Supplementary Tables S2 and S3.

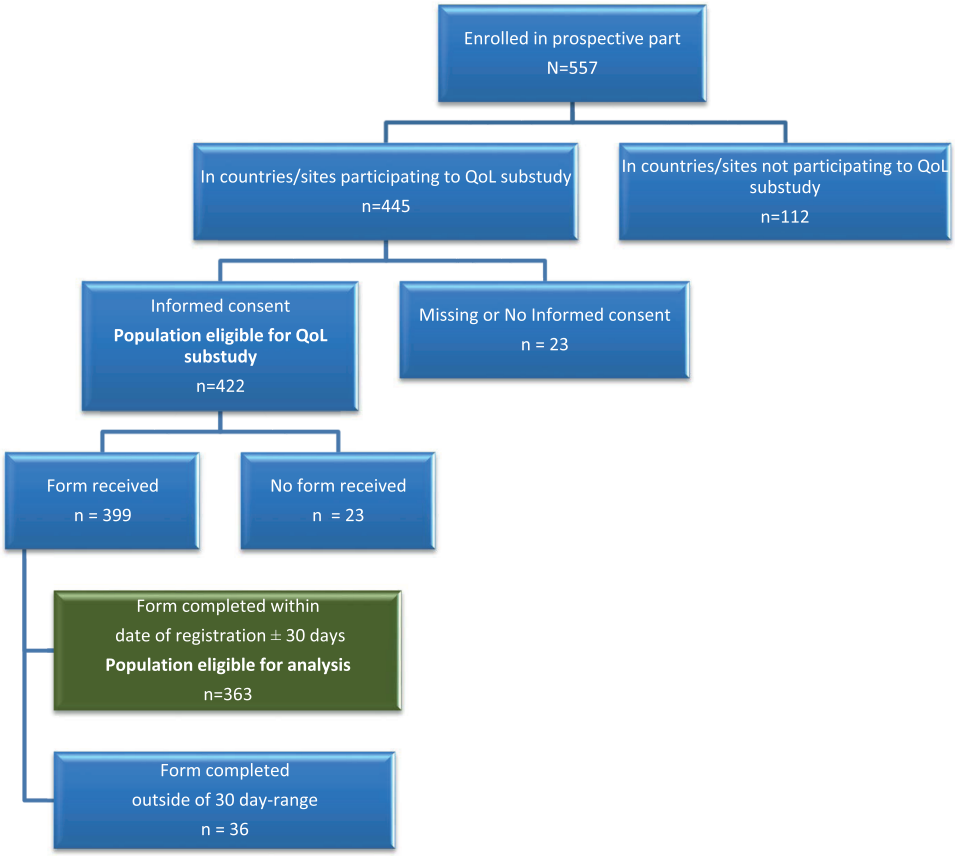

Figure 1. CONSORT diagram.

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Table 1. Baseline characteristics.

	All patients (*N* = 363)
	N (%)
Patient and tumor characteristics	
Year of diagnosis	
1996-2000	2 (0.6)
2001-2005	2 (0.6)
2006-2010	2 (0.6)
>2011	337 (92.8)
Missing	20 (5.5)
Time from diagnosis to QoL form (months)	
Median	11.5
Range	0.5-214.5
Q1-Q3	5.1-25.2
Mean (SD)	18.10 (22.91)
N obs	343
Age at diagnosis	
Median	67.3
Range	32.6-92.3
N obs	343
Age at diagnosis (categories)	
≤40	4 (1.1)
41–50	31 (8.5)
51–65	118 (32.5)
66-75	107 (29.5)
>75	83 (22.9)
Missing	20 (5.5)
M status	
M0	253 (69.7)
M1	28 (7.7)
Mx	82 (22.6)
If M0, LN status (path., clin. if path. is missing)	*N* = 253
Negative	136 (53.8)
Positive	114 (45.1)
Missing	3 (1.2)
Local and systemic treatments	
Surgery to the breast/lymph nodes[a]	180 (49.6)
Breast conserving	9 (5)
Mastectomy	170 (94.4)
Lymph node only	1 (0.6)
Radiotherapy[a]	24 (6.6)
Systemic therapy[a]	70 (19.3)
Chemotherapy	*N* = 70
No	45 (64.3)
Yes	25 (35.7)
Endocrine therapy	*N* = 70
No	18 (25.7)
Yes	51 (72.9)
Targeted therapy	*N* = 70
No	61 (87.1)
Yes	7 (7.1)

Surgery or radiotherapy prior to baseline QoL survey; systemic treatment initiated prior to baseline QoL survey.

Comparison to Reference Groups

Fig. 2A displays the EORTC QLQ-C30 functional scales in patients with male BC compared to those previously found in female patients with BC and in a reference healthy male population. In the historical sample of women with BC, mean global health status score was 61.8 (SD: 24.6) in 2782 women with mixed stage and 65 (SD: 23) in the subgroup of 464 women with stage 1-2 tumors, inferior to those we found in male BC. In a reference population of healthy men, mean global health status score was 71 (SD: 23), comparable to that we identified in men with BC. Mean social functioning scores were 77 (SD: 27) and 88 (SD: 21) in the reference populations of women with BC and healthy men, respectively. Fig. 2B shows the EORTC QLQ-C30 symptom scales in the same populations. Although fatigue, insomnia, and pain were most commonly reported symptoms with highest scores in both male and female BC patients, women's mean scores indicated more burdensome symptoms (mean: 33 [SD: 26], 30 [SD: 32], and 29 [SD: 29] respectively).

Discussion

This study represents a significant step toward an improved understanding of QoL in male BC patients. Unlike previous QoL research focusing on long-term survivors, we have assessed QoL around the time of diagnosis, and we have done so in a diverse, international population from 13 countries using a survey comprised of validated components and translated into multiple languages. This study demonstrates that it is possible to perform international prospective trials in patients with a rare cancer. The relatively high response percentage may reflect an understanding on the part of male BC patients that research is lacking to inform the management of this rare disease.

Importantly, sexual activity is affected by advanced disease stage and age, consistent with another smaller study that surveyed men later in survivorship.[20] However, despite concerns that we might find substantial emotional distress in this population related to sexual dysfunction and having been diagnosed with a cancer that is strongly associated with female gender, there was little evidence of poor emotional or social functioning. Many men had not yet started systemic treatment for their cancers at the time of survey completion, which may account in part for the preserved QoL scores (the side effects of endocrine therapy had not started yet in those cases).

Our data are consistent with the findings of a survey of 84 men recently discharged from one of 51 hospitals in Germany after treatment of primary breast cancer in 2006-2011. Compared to 20 589 women with BC, an adjusted analysis showed that male patients scored significantly better on physical functioning, role functioning-physical and emotional, bodily pain, vitality, social functioning, and mental health. However, compared to healthy men, these men with recently diagnosed BC scored worse, particularly with regard to emotional and physical role functioning.[18,21]

A Dutch study of men with prostate cancer shows that a cancer diagnosis itself, even before treatment begins, can adversely impact HRQoL.[22] In this assessment of 80 men, it was evident that the decision to undergo more aggressive prostate cancer treatment was associated with greater decrements in HRQoL, perhaps because fear of the toxicities of treatment is detrimental to mental health. Interestingly, in other studies

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Table 2. EORTC-QLQ-C30, B23, and PR25 questionnaire data.

	N	Mean (SD)	Median (range)
EORTC-QLQ-C30 functional scales			
Physical functioning	361	85.3 (20.9)	93.3 (0.0-100.0)
Role functioning	361	80.8 (27.7)	100.0 (0.0-100.0)
Emotional functioning	362	77.0 (22.4)	86.3 (0.0-100.0)
Cognitive functioning	362	87.3 (17.6)	100.0 (0.0-100.0)
Social functioning	362	84.9 (22.1)	100.0 (0.0-100.0)
Global health status/ QoL	362	73.4 (20.8)	75.0 (0.0-100.0)
EORTC-QLQ-C30 symptom scales			
Fatigue	362	21.7 (23.8)	11.1 (0.0-100.0)
Nausea/vomiting	362	3.4 (12.4)	0.0 (0.0-100.0)
Pain	362	15.8 (22.7)	0.0 (0.0-100.0)
Dyspnoea	361	13.1 (23.3)	0.0 (0.0-100.0)
Insomnia	360	21.5 (28.4)	0.0 (0.0-100.0)
Appetite loss	358	8.0 (18.6)	0.0 (0.0-100.0)
Constipation	362	8.1 (20.1)	0.0 (0.0-100.0)
Diarrhoea	359	5.7 (16.0)	0.0 (0.0-100.0)
Financial problems	362	11.5 (23.9)	0.0 (0.0-100.0)
EORTC-QLQ-BR23 functional scale			
Future perspectives	354	62.0 (29.5)	66.7 (0.0-100.0)
EORTC-QLQ-BR23 symptom scales			
Systematic therapy side effects	359	8.9 (12.4)	4.8 (0.0-85.7)
Breast symptoms	357	17.6 (17.7)	16.7 (0.0-100.0)
Arm symptoms	357	12.8 (19.0)	0.0 (0.0-100.0)
Upset by hair loss	31	22.6 (26.4)	33.3 (0.0-100.0)
EORTC-QLQ-PR25 functional scales			
Sexual activity	347	31.0 (25.6)	33.3 (0.0-100.0)
If sexually active, sexual functioning	168	79.6 (17.8)	83.3 (25.0-100.0)
EORTC-QLQ-PR25 symptom scale			
Hormonal symptoms	360	7.8 (9.7)	5.6 (0.0-61.1)

High scores for functioning and global health/QoL measures indicate high/healthy levels of functioning/high QoL. High scores for symptom-focused measures indicate a high level of symptoms/problems.

focused on long-term survivors of prostate cancer, HRQoL does not seem to differ substantially by treatment.[23]

Limitations of our study include the unavailability of a validated questionnaire specifically designed for men with BC. We used the extensively validated EORTC QLQ-C30 and also added the adapted EORTC QLQ-BR23, plus select items from the QLQ-PR25, to capture the experiences of men with BC, including with regard to sexual functioning (for which the BR23 does not apply to men) and side effects of endocrine therapy. Although the EORTC QLQ-C30, BR23, and PR25 were already fully validated in all of the languages we needed for this study, the resulting merged questionnaire has not yet been validated. Of note, the ongoing EORTC QLG 002/2019 study aims at developing a male BC specific BC module, based on input from male BC patients and health care professionals to determine which issues are most relevant for this patient group. Another limitation is that inclusion was not based on diagnosis date, so some patients had already received treatment at the time of the survey. Although, as expected, treatments consisted mostly of surgery and to a lesser extent radio- or systemic therapy, this could have affected symptoms and QoL. The lack of substantial differences in QoL or symptom burden between those with advanced stage and those with early-stage disease should be interpreted with caution in light of the relatively low number of patients with advanced disease. Furthermore, comparing male BC to female BC has its limitations. The EORTC QoL female reference population had different characteristics (62% were under age 60; 41% had recurrent or metastatic disease, 31% had stage 1-2 disease, and 29% had unknown stage). In our study, 8% of patients had known advanced disease and 23% had unknown stage. These differences in stage could have resulted in patient-reported QoL differences. Also, differences in BC management, such as the low rate of breast conservation in men, may have influenced symptoms. Nonetheless, gender differences in QoL scores independent of breast cancer may contribute to differences between patients with female and male BC. This has been observed also in other tumor types. Therefore, comparisons of these QoL and symptom data to historic controls should be regarded as only hypothesis-generating. However, they help to integrate our results with other existing data about QoL.

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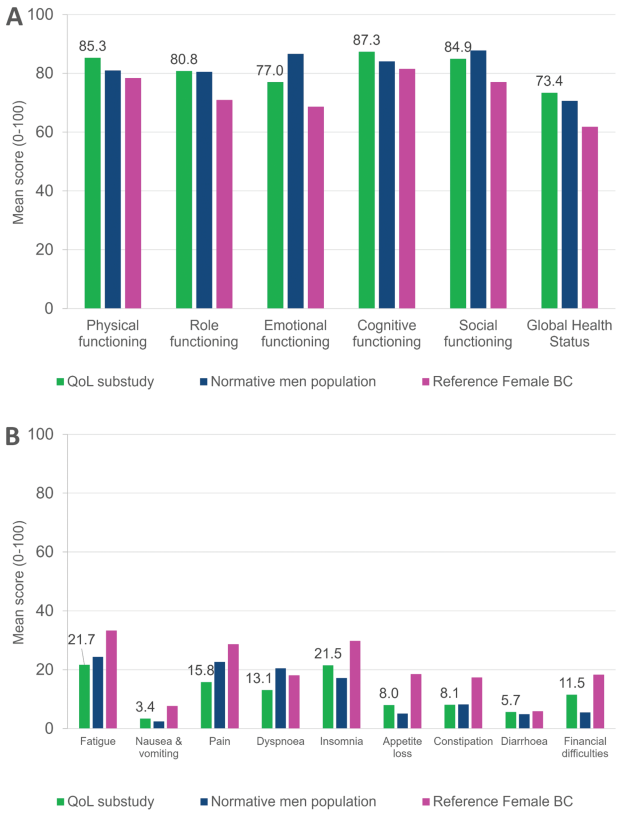

Figure 2. (**A**) EORTC QLQ-C30 functional scales in male patients with BC, a healthy male reference population, and female patients with BC. High scores indicate high/healthy levels of functioning. (**B**) EORTC QLQ-C30 symptom scales in male patients with BC, a healthy male reference population and female patients with BC. High scores indicate a high level of symptoms/problems.

Conclusion

This large prospective registry substudy demonstrates that overall QoL is good in men who were recently diagnosed with breast cancer, but some still suffer appetite loss, fatigue, and insomnia. Sexual functioning may also be an issue. In our future analyses of later surveys, the impact of specific treatments on changes in symptoms and QoL over time will be assessed. It will be important to use the data collected via this and our upcoming serial QoL assessments to help develop interventions to improve clinical care for men with breast cancer.

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Conflict of Interest

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Author Contributions

Conception/design: C.P.S., E.v.L.S., F.C., A.C.W., V.B.R., C.C., S.H.G., K.J.R. Provision of study material or patients: C.P.S., E.v.L.S., F.C., B.L., A.C.W., V.B.R., G.W., M.H.A., I.B.S., I.H., A.H.H., M.L., D.M., N.S.R., T.J.S., A.W.G.v.d.V., C.V.P., M.M.V., R.L.Y., S.H.G., K.J.R. Collection and/or assembly of data: C.P.S., E.v.L.S., F.C., C.P., C.C., S.H.G., K.J.R. Data analysis and interpretation: C.P.S., F.C., C.P., C.C., K.J.R. Manuscript writing: C.P.S., K.J.R. Final approval of manuscript: All authors.

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Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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Supplementary Material

Supplementary material is available at *The Oncologist* online.

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