Journal of Oncology

Patient reported outcomes and experience in elderly women with breast cancer

Lead Guest Editor: Giuseppe Colloca
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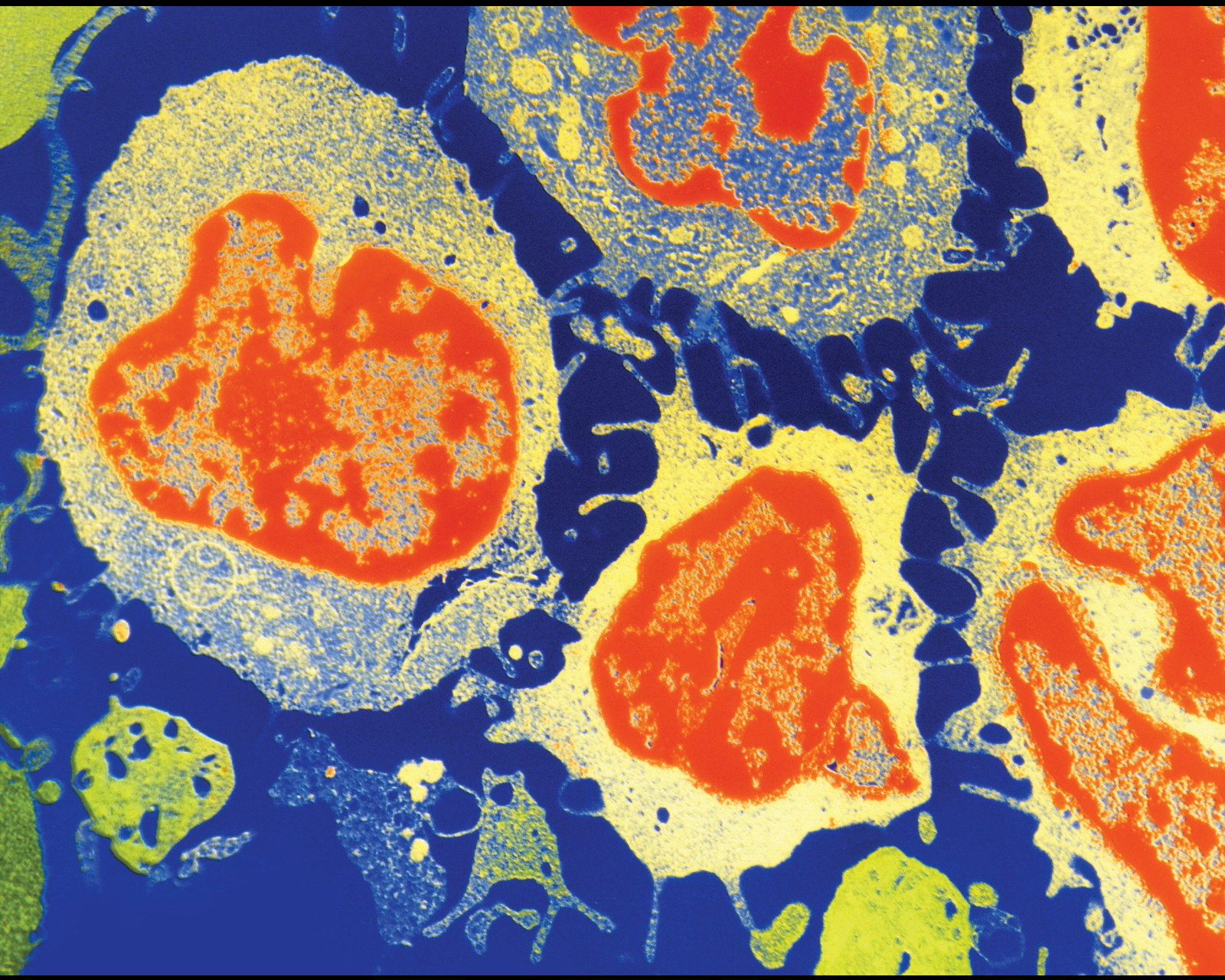

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Review Article

Could a Personalized Strategy Using Accelerated Partial Breast Irradiation be an Advantage for Elderly Patients? A Systematic Review of the Literature and Multidisciplinary Opinion

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Introduction. Elderly patients are underrepresented from a majority of clinical trials and the choice of the best treatment becomes a challenge. The optimal treatment should be personalized and based on a multidisciplinary approach that includes radiation oncologists, surgeons, geriatricians, medical oncologists, social workers, and support services. The global evaluation of the patients and the creation of nomograms may facilitate the definition of long-term treatment benefits minimizing the use of unnecessary therapy. *Material and Method*. A systematic research using PubMed, Scopus, and Cochrane library was performed to identify full articles analyzing the efficacy of APBI in elderly patients with breast cancer. ClinicalTrials.gov was searched for ongoing or recently completed trials, and PROSPERO was searched for ongoing or recently completed systematic reviews. *Results*. Seven papers fulfilled the eligibility criteria. The number of evaluated patients was 405 and the median age was 77.7 years. The disease-free survival (DFS) range was 96.1%–100%, the grade 3-4 toxicity range was 0%–6.6%, the cancer-specific survival (CSS) range was 97.9%–100%, and the overall survival (OS) range was 87%–100%. All studies reported excellent/good cosmetic results in a range of 74% to 99%. *Conclusion*. Accelerated partial breast irradiation (APBI) results in a safe and effective substitute for the adjuvant external beam radiotherapy in selected elderly early-stage breast cancer patients. Based on the relatively low toxicity, APBI should be advised in selected patients with life expectancies larger than 5–10 years.

1. Introduction

Breast cancer is the most common cancer in women, and the risk to develop breast cancer increases with age. Indeed 21% of all cases and 13% of breast cancer mortality occur in patients aged ≥70 years old [1]. Despite this data, elderly patients are underrepresented from a majority of clinical trials and the choice of the best treatment becomes a challenge. A great need remains for studies providing evidence levels to guide the treatment of elderly patients, which is often not guideline adherent. Patients aged 70 years and over, who are in good health condition, have a median life expectancy of 15.5 years and half of them will live much longer. Treatment decisions should not be based on age alone but need to ensure that older patients get the best quality of care [2, 3]. There is growing awareness that

functional age is a more accurate indicator of cancer treatment compliance because it differs between patients with the same chronologic age [4, 5]. Furthermore, consensus guidelines and position statements recommend the use of the geriatric assessment in elderly patients with cancer [6, 7] in order to avoid worsening of global quality of life.

The optimal treatment should be personalized [8–11] and based on a multidisciplinary approach that includes radiation oncologists, surgeons, geriatricians, medical oncologists, social workers, and support services. In this way, we can obtain an informed discussion of the estimated benefits and risks of cancer treatment. The global evaluation of the patients and the creation of nomograms [12, 13] may facilitate the definition of long-term treatment benefits minimizing the use of unnecessary therapy.

Several randomized trials [14–17] have shown the safety of omitting radiotherapy, however, with little impact on clinical practice [18–20], because there are subgroups of fit older patients where radiotherapy cannot be systematically omitted [21–23]. The impact of local relapse on quality of life should be considered when radiotherapy is intended to omit [24, 25]. To overcome this problem and to prevent undertreatment, accelerated partial breast irradiation (APBI) can be considered an alternative to conventional external beam radiotherapy or exclusive hormonal therapy because it improves convenience for women with low-risk tumors [26–35]. Moreover, the side effects of hormonal therapy can modify the quality of life and patients' reported outcomes during follow-up without a real benefit on overall survival [26–35].

The present systematic review was performed to assess the effectiveness and outcomes of APBI in the adjuvant treatment of elderly patients with breast cancer.

2. Materials and Methods

A systematic research using PubMed, Scopus, and Cochrane library was performed to identify full articles analyzing the efficacy of APBI in elderly patients with breast cancer. ClinicalTrials.gov was searched for ongoing or recently completed trials, and PROSPERO was searched for ongoing or recently completed systematic reviews. The studies were identified through the following medical subject headings (MeSH) and keywords including "breast cancer", "brachytherapy", "elderly", and "palliation". The search was restricted to the English language. The Medline search strategy was ("Brachytherapy" [Mesh] OR "Brachytherapy" [All Fields]) AND ("Breast Neoplasms" [Mesh] OR "Breast neoplasms" [All Fields] AND "Aged" [Mesh] OR "Aged" [All Fields]). To avoid missing relevant studies, we chose this strategy with high sensitivity but low specificity.

We analyzed only clinical full-text studies of elderly breast cancer patients treated with APBI alone. Conference papers, surveys, letters, editorials, book chapters, and reviews were excluded. Time restriction (1990–2018) as concerns the years of the publication was considered.

Two independent radiation oncologists expert in radiotherapy for breast cancer (VL expert in interventional radiotherapy and VM expert in external beam radiotherapy) screened citations in titles and abstracts to identify appropriate papers. Eligible citations were retrieved for full-text review. Uncertainties about their inclusion in the review were controlled by an expert multidisciplinary team composed by a radiation oncologist expert in interventional radiotherapy of another institution (GK), a surgeon (GG), a medical and radiation oncologist (FM), and a geriatric (GC). Finally, an expert committee (VV, MAG, and LT) performed an independent check and the definitive approval of the review.

The primary outcome was the disease-free survival after APBI during follow-up. Secondary outcomes included specific cancer survival, overall survival, and adverse event rates.

A summary table (Table 1) was created including mono/multicentric study, sample size, median age, disease-free survival (DFS), toxicity, cancer-specific survival (CSS), and overall survival (OS).

3. Results

The literature search resulted in 420 articles (Figure 1). After the screening of the titles, abstracts, and language of these references, 378 studies were excluded, and 16 full-text articles were selected. Of these, 7 papers fulfilled the eligibility criteria.

Only one study is randomized [36], two studies are phase II [37, 38], and 4 studies are retrospective investigations [39–42]. Following the defined selection criteria, only data from the APBI treatments in elderly patients were extracted and considered for the analysis. The number of evaluated patients was 405 and the median age was 77.7 years. The DFS range was 96.1%–100%, the grade 3-4 toxicity range was 0%–6.6%, the CSS range was 97.9%–100%, and the OS range was 87%–100%.

Table 1 lists the characteristics of the included studies.

All studies reported excellent/good cosmetic results in a range of 74% to 99%.

4. Discussion

Elderly breast cancer represents one of the main public health issues, which will become more critical with the increasing life expectancy. Patients aged 70 years and over who are in good health condition have a median life expectancy of 15.5 years and half of them will live much longer [43, 44].

Optimal treatment decisions should not be based on chronological age alone, but need to ensure that elderly patients get the best possible quality of care. The presence of other characteristics (concurrent comorbid illnesses) that represent potential causes of mortality must also be considered to identify those women who are unlikely to die of breast cancer and for whom the omission of adjuvant treatment may be the best option. A geriatric assessment should be mandatory because it provides specific and overall information about the health status, focusing on somatic, functional, and psychosocial domains, which is necessary to provide a multidisciplinary treatment plan [45].

Table 1: Characteristics of the included studies.

Author	Period	Study	Sample size, *n*	APBI	Median age, years	DFS	Toxicity (G3-G4)	CSS	OS
Cozzi et al. [39]	2006–17	Retrospective	86	HDR-IRT	82 (44–92)	Recurrent at 3 years: 96% Primary at 3 years: 97.8%	5.6%	100% at 3 years	Recurrent at 3 years: 87% Primary at 3 years: 89%
Genebes et al. [40]	2005–16	Retrospective	70	HDR-IRT	80.7 (62–93.1)	97.6% at 5 years	0%	97.9% at 5 years	93.2% at 5 years
Hannoun-Lévi et al. [37]	2012–14	Phase II	26	HDR-IRT	77 (69–89)	100% at 3 years	0%	100% at 3 years	95.2% at 3 years
Hannoun-Lévi et al. [38]	2004–08	Phase II	40	HDR-IRT	74 (70–87)		2%	100% at 3 years	100% at 3 years
Kinj et al. [41]	2012–15	Retrospective	45	HDR-IRT	77.7 (65–92)	100%,	6.6%	100%, at 3 years	93.1% at 3 years
Meattini et al. [36]	2005–13	Randomized phase 3	58 EBRT 59 APBI	IMRT	EBRT 74.1 (70.0–83.2) APBI 74.4 (70.1–85.3)	EBRT 96.1% at 5 years APBI 98.1% at 5 years	EBRT 5.1% APBI 1.7%	100% at 5 years	
Sumodhee et al. [42]	2005–16	Retrospective	79	HDR-IRT	77 (66–89)	97.4% at 10 years	0%	98.1%	

APBI: accelerated partial breast irradiation; HDR-IRT: high dose rate interventional radiotherapy; IMRT: intensity-modulated radiotherapy; EBRT: external beam radiotherapy; DFS: disease-free survival; CSS: cancer specific survival; OS: overall survival.

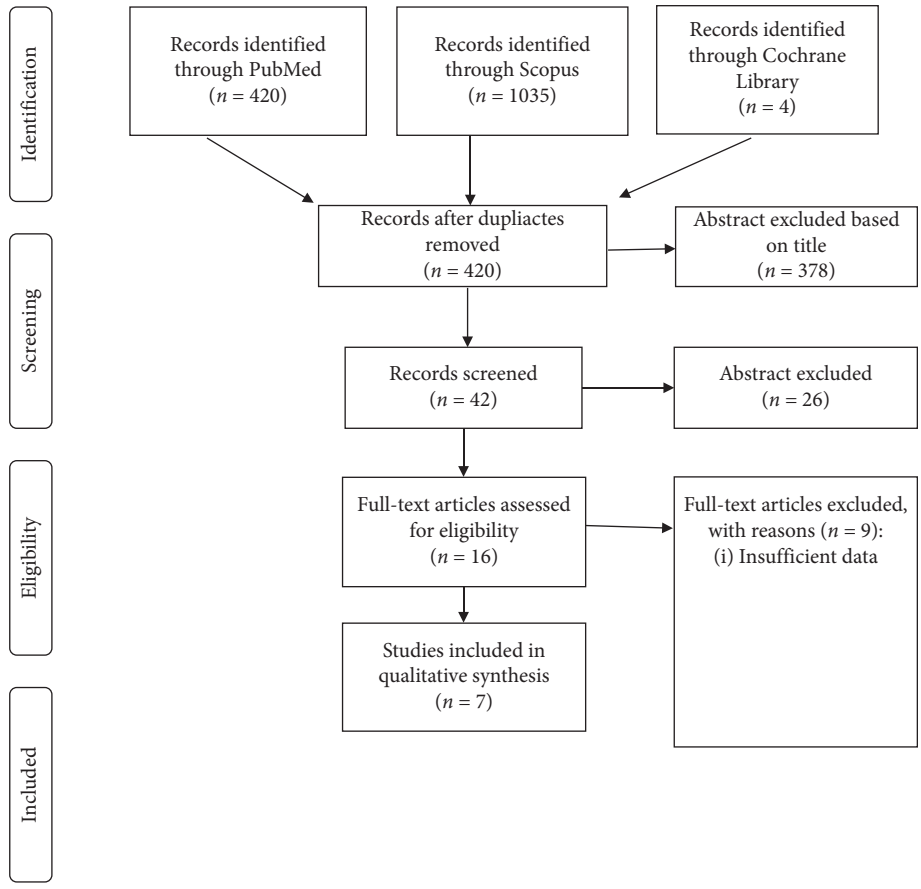

Figure 1: PRISMA flowchart for the outcome and late adverse effects.

Unfortunately, only a limited number of studies have focused on the role of geriatric assessment in treatment decisions for older early breast cancer patients [46]. It is well known that elderly women are undertreated with breast-conserving surgery (BCS) in favor of mastectomy [47, 48]. There are many reasons for this, such as logistical concerns

related to radiotherapy, the possibility of comorbidity, functional impairment, frailty, ideas about body-image, among others.

Furthermore, relatively few elderly patients are accrued in clinical trials. Barriers to the accrual of elders include "physician bias" based on the fear that the patient will not tolerate or will not benefit from the treatment and "patient and family members bias" based on the belief that treatment is not worthwhile or is too toxic. The treatment of elderly breast cancer patients often does not comply with guidelines and older women may receive less of adjuvant radiotherapy following BCS and variably more hormonal therapy. For this reason, for elderly patients with early breast cancer, the choice of the appropriate adjuvant treatment remains challenging.

Multiple trials over the years have investigated the role of RT and TAM in low-risk breast cancer patients in terms of local recurrence (LR), metastases disease-free survival (DMFS), and OS [49–53] and the possibility of avoiding RT [14–17]. Sole adjuvant endocrine or radiotherapy seems to be equivalent to all important oncological endpoints. Endocrine therapy is frequently associated with fatigue symptoms and possible severe side effects like thromboembolic events, endometrial cancer related to tamoxifen, as well as osteoporosis, cardiovascular disease, and arthralgia related to aromatase inhibitors. In contrast to radiotherapy at least 5 years lasting endocrine therapy, the typical side effects of a three-week hypofractionated adjuvant radiotherapy course, like low-grade erythemas and minor edemas, appear relatively moderated and are of short duration [54]. Moreover, it is important to keep in mind that personalized treatment decisions should be based on the patient's baseline risk of recurrence. Indeed, there is strong evidence that the addition of radiotherapy reduces the risk of breast and axillary recurrence and this effect is maintained at 10 years, while radiotherapy does not significantly affect distant recurrence or overall survival rates in patients over 70 years old [14–17].

Moreover, it is important to consider the adherence of patients to endocrine therapy: given the associated adverse effects including hot flashes, thrombotic events, bone loss, and joint pain/stiffness, several studies reported a dropdown of treatment adherence up to the rate of 67% in the first year of treatment, with a further reduction up to 30% in the fifth year [55, 56]. In the longer term, the potential effect of a local relapse on quality of life and the psychological state in older patients should not be underestimated.

An important issue to consider is that not all patients 70 or older are the same. A healthy 70-year-old woman has a high chance of living for more than 10 years, risking a one-in-10 rate of local recurrence if radiotherapy is omitted and a one-in-50 rate if radiotherapy is given. Conversely, in patients with significant comorbidities, the benefit of endocrine therapy can be questioned: the survival benefit of systemic treatment in patients with low-risk tumors is seen after 5 years, whereas the benefit of radiotherapy in reducing local recurrence is considerable in the first 5 years with a survival benefit at 15 years. In this subgroup of patients, perhaps endocrine therapy and not radiotherapy can be omitted.

The omission of radiotherapy may be proposed in low-risk breast cancer patients with limited life expectancy below 5 years. As most patients will present with substantially longer life expectancies, individual counseling about the risks and benefits of radiotherapy, based on clinical and biological features, is strongly recommended. Thus, there is no subgroup of fit older patients in whom post-BCS RT can be systematically omitted.

Since resistance to RT omission persists even in selected cases due to the risk of local recurrence and the availability of alternative forms of RT, APBI may consider a valuable compromise between EBRT and exclusive endocrine therapy.

Particularly in elderly patients, APBI presents many advantages like the possibility of delivering higher doses in the area of the tumor bed and in the same time reducing the dose to the normal breast tissue and adjacent organs at risk [57]. Additionally, a shorter treatment time might improve the convenience and quality of life of the patients, possibly reducing the physical and psychological stress related to radiotherapy [58–60]. These all increase their adherence and reduce the likelihood of inappropriate mastectomy [61–63]. Finally, APBI may reduce the total costs of treatment depending on the used modality [64]. There are many available techniques to perform APBI including intraoperative radiotherapy (IORT), three-dimensional or intensity-modulated EBRT involving stereotactic capabilities, or interventional radiotherapy (IRT). Careful patient selection is an important element to define which patients are suitable for APBI. Four published consensus statement criteria can help the radiation oncologist in this choice (ASTRO: American Society for Radiation Oncology; GEC-ESTRO: Groupe Europeén de Curiethérapie-European Society for Radiotherapy and Oncology; ABS: American Brachytherapy Society; ASBS: American Society of Breast Surgeons) [26–29]. Four phase III randomized trials on APBI have been published up to date, but none of these was specifically designed for older women [30, 31, 33, 34], and no comparison can be made with other trials in which the omission of radiation therapy has been investigated [15].

The 7 studies reported in this review showed excellent rates of DFS (range 96%–100%), CSS (97.9%–100%), and OS (87%–100%) with acceptable G3 toxicities (range 0%–6.6%). Moreover, all studies reported an excellent/good cosmetic result range 74%–99%.

Personalized assessments of the risk benefits are essential when considering older patients for adjuvant treatment after breast-conserving surgery. The use of large databases and nomogram could help for improved analysis of the outcomes in these populations [65–69].

5. Conclusions

APBI results in a safe and effective substitute for the adjuvant EBRT in selected elderly early-stage breast cancer patients. It is more convenient for high-volume radiation centers with long waiting lists and for patients who live far away from RT centers. Radiotherapy departments have to be aware of this issue, to provide the best therapeutic option combining

optimal local control with good quality of life in a cost-effective way. The actual choice of APBI techniques will be influenced by many factors whereby the strongest arguments are local experience and hospital budget size.

However, one of the most important considerations is to select the most appropriate patient population for this treatment strategy and this should be performed in experienced and trained hands.

In aged or frail patients, a comprehensive assessment of the overall health status is recommended when weighing the expected absolute benefits of cancer treatment against tumor biology, potential toxicities, physiological age, patient preference, quality of life, and remaining life expectancy.

Based on the relatively low toxicity, APBI should be advised in selected patients with life expectancies larger than 5–10 years.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Research Article

Italian Men Tested for BRCA1/2 Mutation: Psychological Distress during 6-Month Follow-Up

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Introduction. Male breast cancer (MBC) is a rare disease, whose main risk factor is genetic vulnerability. Despite care of men with MBC is modeled on care of women, men's experiences with the disease and concerns related to the status of genetic mutation carrier are unique. So far, little is known concerning the psychological impact in BRCA1/2 testing, especially with regard to specific subset of individuals, such as male subjects and the elderly. *Methods*. We assessed self-reported anxiety and depression levels in 26 male subjects presenting at Unit of Breast Surgery in Breast Unit of AOUI Verona (MBC patients, $n = 7$; high-risk unaffected subjects, $n = 19$). We specifically examined the scores obtained by these subjects in the HADS questionnaire administered before and 6 months after the genetic testing for BRCA gene mutations. *Results*. Among the 17 unaffected men tested, 7 (41%) received a positive test (either BRCA1 or BRCA2 pathogenic variant) and 10 (59%) a negative test. Of the 9 MBC patients tested, only one subject received a positive test result. No significant differences were observed in mean scores, mean change from baseline to follow-up, either for those with *T*+ or T− test results. *Discussion*. Genetic testing for BRCA1/2 mutation was not associated in our sample with increased level of psychological distress as measured with HADS in a short-term evaluation.

1. Introduction

Male breast cancer (MBC) is a rare disease, comprising only 0.1% of all men cancers [1] and about 1% of all breast cancer [2], while female breast cancer (FBC) comprises 25% of all cancers in females [3].

MBC tends to be diagnosed in later life, at a more advanced stage, and is considered similar to late-onset (postmenopausal) FBC [4]. Genetic vulnerability is a shared risk for MBC and FBC, and the most relevant risk factors are a family history of BC and the presence of pathogenic variants of BRCA gene [4].

Despite care of men with MBC is labeled on women's care, men's experiences with the disease and concerns related to the status of genetic mutation carrier are unique [4, 5].

Several studies focused on the short- and long-term psychological impacts of breast cancer on women [4] and other forms of cancer in the male and female population [6]. Given the rarity of MBC, a thorough understanding of the psychological implications of this condition is still lacking. Two relevant English studies aimed at deepening the experience and the psychological impact of MBC, through combination of tools for assessing general distress and cancer-specific distress, such as the Hospital Anxiety and Depression Scale (HADS) [7, 8] and Impact of Event Scale (IES) [7, 8]. Body image changes, measured using the Body Image Scale (BIS) [7], and coping strategies had also been evaluated [7, 8]. Another study on MBC survivors reported that 8% and 5% of the sample met the standard criteria for anxiety and depression [5].

Since the introduction in clinical practice of genetic testing for BRCA1/2 gene mutations, there has been a rising interest in eventual psychological distress caused by testing [9]. So far, no definite conclusions emerged and there is still a need for empirical evidence concerning the psychological impact of BRCA1/2 testing, especially with regard to specific subset of individuals, such as male subjects and the elderly.

Considering the gradual increase in MBC incidence [1, 2], it seemed appropriate and perhaps a bit provocative,

to focus our attention on men suffering from this condition or at high-risk of developing it. Moreover, psychological features related to genetic testing for BRCA1/2 mutations have never been investigated in a population of Italian males.

The aim of this retrospective study is to assess self-reported anxiety and depression levels in male subjects presenting at Unit of Breast Surgery in Breast Unit of AOUI Verona. We specifically examined the scores obtained by these subjects in the HADS questionnaire administered before the genetic testing for BRCA gene mutations and during a 6-month follow-up visit.

2. Materials and Methods

This is a retrospective analysis of all male patients presenting with MBC and high-risk not-affected men, between 01/11/2015 and 31/01/2018, at the Unit of Breast Surgery at Verona AOUI. In our retrospective study were enrolled male subjects with a personal or family history of MBC, male subjects with a family member carrier of BRCA1/2 gene mutation, male subjects with a close family member diagnosed with female breast cancer (FBC) at 45 or younger, male subjects with a close family member diagnosed with bilateral breast cancer at any age, male subjects with three or more close family members diagnosed with breast cancer at any age, and male subjects with a close family member diagnosed with pancreatic cancer or metastatic PCa at any age or family history of ovarian cancer, pancreatic cancer, aggressive PCa, or metastatic PCa. Female subjects, male subjects affected by benign breast tumors, and healthy men with a family history not suggestive of genetic mutations linked to breast cancer were excluded.

Clinicopathological, psychological, and genetic data were obtained from Breast Unit Database (Gecos, Cartelle2000, DataBreast), which collects patients' and high-risk subjects' clinical records since January 1992. No additional tests were performed.

We registered male subjects' following data: current age, age at breast cancer diagnosis, breast cancer stage and treatment, family history of breast, ovarian, or prostate cancer in firstdegree relatives and BRCA 1/2 mutation status (if available), and psychological distress (HADS, Hospital Anxiety and Depression Scale). For MBC patients, we also recorded alcohol consumption and smoking habits, comorbidities, and history of psychological symptoms.

Patients diagnosed with MBC and high-risk not-affected men were candidated to be examined by an expert geneticist, specifically dedicated to the study of hereditary breast, ovarian, and prostate cancer. During ambulatory interview, the geneticist drawn genealogical family trees based on participants' family history. The BRCA test was performed through a blood sample collected at the Brest Unit and sent to the Medical Laboratory Department, where it was validated by fluorimetry technique and multiplex polymerase chain reaction (PCR). BRCA1 and BRCA2 mutations were classified according to their potential functional effect as recorded in the Breast Cancer Information Core (BIC) database [10] as class, 5 pathogenic; class 4, likely pathogenic; class 3, uncertain; class 2, likely not pathogenic; and class 1, not pathogenic.

Participants' psychological distress was assessed through the HADS at the time of testing for BRCA1/2 gene mutation and during a 6-month follow-up visit [11]. This is a four-point 14-item self-report instrument to assess anxiety (seven items) and depression (seven items) in somatic, psychiatric, primary care patients and in the general population [12]. Each item is scored from 0 to 3, so that the maximum for each subscale is 21. Cutoff points were lower than 8 (within normal range), 8 to 10 (possible clinical cases), and ≥11 (clinical cases) for both scales, respectively [11]. The HADS was translated into Italian and validated by Costantini et al. in a sample of cancer inpatients [13]. They also showed the validity of the total score as a reliable measure of general distress [13], so that the Italian version can be used as a screening questionnaire for people at increased risk of developing psychological or psychiatric conditions.

All collected data were recorded in a Microsoft Office Excel spreadsheet.

Continuous variables are expressed as mean and standard deviation. When comparing two groups with normal distributions, we applied *t*-tests for independent and paired samples. Nonparametric tests were used when appropriate due to skewed distributions or low patient numbers. All statistical analyses were performed with IBM SPSS 10.0.

3. Results and Discussion

We collected data on 26 male subjects, who presented at our center between November 2015 and January 2018, were eligible for BRCA testing and received either a positive result (carriers) or a negative result (noncarriers).

The mean age of participants was 58 years (SD = 12), seven subjects were >65 years of age. Thirty-five per cent of the subjects tested had been treated for MBC, while sixty-five per cent were unaffected subjects with strong family history for breast cancer; among them, 5 had other cancer than MBC (prostate cancer).

All the nine subjects affected by MBC underwent modified radical mastectomy, before genetic testing. Among those with MBC, 3 subjects were diagnosed with early-stage MBC (Ia-Ib) and were administered ormonotherapy and 6 subjects were administered chemotherapy plus ormonotherapy due to advanced cancer stage at diagnosis.

From January 2015 to January 2018, 26 men (7 MBC patients and 19 high-risk not-affected men) were engaged in genetic counseling and testing at our center and completed the HADS questionnaire in paper format prior to genetic testing and during a 6-month follow-up visit. Baseline characteristics of participants are shown in Table 1.

Between those with available data, namely, MBC patients, only one subject reported history of psychological symptoms. Most of the MBC patients (66%) had significant medical issues, such as hypertension, diabetes mellitus, or other cardiovascular diseases. Participants received genetic testing results between 2 and 4 weeks after completion of baseline assessment and were engaged in a 6-month follow-up visit. 8 subjects (30.8%) were found to be carriers and 18

Table 1: Baseline characteristics of MBC subjects and unaffected men in our sample.

	Unaffected men ($n = 17$) Mean (SD)	MBC subjects ($n = 9$) Mean (SD) or frequency (%)
Age (years)	51.8 (13.2)*	60.7 (7.0)*
HADS-A	3.5 (3.1)**	5.7 (3.1)**
HADS-D	2 (2.0)*	3.5 (1.9)*
Alcohol consumption[1]	N/A	2 (22%)
Smoking status	N/A	4 (44%)
Psychological symptoms	N/A	1 (11%)
Relevant comorbidities	N/A	6 (66%)
Other cancer	N/A	1 (11%)

*$P < 0.05$; **$P = 0.05$. [1]>20 g/day.

noncarriers of BRCA1/2 gene mutation. Among the 17 unaffected men tested, 7 (41%) received a positive test (either BRCA1 or BRCA2 pathogenic variant) and 10 (59%) a negative test. Of the 9 MBC patients tested, only one subject received a positive test result.

Self-rated levels of anxiety and depression were recorded with the HADS in 19 subjects, both prior to genetic testing and during follow-up visit 6 months after carrier status disclosure. 7 subjects failed to complete the HADS questionnaire after receiving genetic testing results, so only baseline assessment data were available.

The affected and unaffected groups were divided into two subgroups (T+ and T−) according to their test results. No significant differences were observed in mean scores, mean change from baseline to follow-up, either for those with T+ or T− test results. Because of this lack of significant differences, only the findings on psychological distress for the unaffected group are shown (Table 2).

In our sample, 5 men (19%) were scored as possible cases of anxiety disorder at baseline. These subjects obtained a nearly significant decrease in the anxiety score from 9 (SD 1.2) to 4.4 (SD 3.8) ($P = 0.06$), after receiving a negative test.

No significant difference in the self-reported distress level as measured with the HADS was detected between adult and elderly subjects.

Table 2: Baseline and follow-up scores of men without cancer, receiving positive and negative BRCA1/2 test results.

	Men without cancer, negative test ($n = 10$)		Men without cancer, positive test ($n = 7$)	
	Baseline Mean (SD)	Follow-up Mean (SD)	Baseline Mean (SD)	Follow-up Mean (SD)
HADS-A	3.4 (3.2)	1.6 (2.2)	3.6 (3.3)	5 (0.5)
HADS-D	2.3 (2.4)	2.1 (2.3)	1.6 (1.5)	1.5 (1.7)

4. Discussion

The main finding of our study is that genetic testing, carried out in a sample of men either affected or at high-risk for MBC, was not associated with increased level of psychological distress as measured with the HADS in a short-term evaluation. Furthermore, our data show that receiving either a positive or a negative result does not affect the level of self-reported psychological distress in a sample of high-risk unaffected men. In our sample, though small, there were no significant differences between adults and the elderly.

A relevant role in MBC pathogenesis is played by genetic risk factors; many studies showed that 15–20% of male patients with BC have a family history of breast cancer, a higher percentage than what observed in women with BC (7%) [14–16]. Accordingly, among our patients was recorded a high percentage of positive family history of BC, i.e., 42.3%. Among genetic risk factors, BRCA 1/2 gene mutations are widely recognized as relevant in MBC susceptibility [17]. In our case series, BRCA gene testing was carried out following ASCO recommendations on BRCA testing [14] in 26 male subjects presenting at our department between January 2016 and December 2018. Among them, 7 were diagnosed with MBC and 19 were healthy high-risk men.

The finding that nearly 31% of participants received a positive test is not surprising because we specifically selected for oncogenetic counselling high-risk subjects, following the ASCO recommendations mentioned above [14]. In this way, we were able to obtain a BRCA gene mutational study of some high-risk family clusters and therefore to involve these subjects in personalized screening programs, which include clinical breast examination, mammography, and contrast-enhanced MRI yearly, as well as clinical urologic examination, serum PSA level testing, and transrectal US for prostate evaluation yearly.

Numerous studies claim that, although to a lesser extent than women, men also expresse a certain degree of psychological distress linked to neoplastic disease [5]. Indeed, despite small sample size, our results show significantly higher mean scores on HADS-A and HADS-D in the affected than in the unaffected group. This result is in accordance with that reported by Reichelt et al. in a retrospective study conducted in 287 Norwegian women [19]. Ruddy et al. evaluated quality of life and symptoms in 42 MBC subjects and implemented the HADS for psychological distress assessment [5]. They found a 40% prevalence of abnormal scores, with 32% in HADS-A and 8% in HADS-D [5]. This finding is much better than ours, but it must be considered that our sample consists mainly of high-risk healthy subjects, which achieved lower average scores compared to affected subjects.

Both men with and without a personal history of MBC showed stable levels of depression and anxiety, measured by the HADS. These scores were either lower than or comparable to those of normative samples [18]. The finding of a sample mean lower than the normative mean of depressive

symptoms could be attributed partly to the fact that the normative data used in this setting were derived from populations of a different nationality than the Italian one, for which normative data are not currently available. An alternative explanation could be that members of families in which there have been numerous cases of neoplastic diseases, develop resilience to stress and a positive elaboration of the concept of illness. Another alternative may be that the counselling and care they had received made them feel safe and that they believed the surveillance programs could provide them and their relatives with the best prevention and care strategies.

We found no significant variation in HADS-A and HADS-D scores from baseline to follow-up in men without cancer receiving either positive or negative BRCA1/2 test results. This finding seems to support the hypothesis that, in this population, test results do not influence the level of distress to any significant degree in short-term evaluation. This result is concordant with that of Reichelt et al. [19], who suggested that stability in mean scores of HADS in Norwegian women indicates a lack of significant traumatization in relation to genetic testing results. Schwartz et al. reported a significant reduction in psychological distress in women tested negative for BRCA1/2 mutation [20]; in our study, genetic testing did not appear to influence HADS scores very much. This difference could be to some extent imputed to the normal/below normal levels of distress at baseline recorded in our sample.

Our results support the main conclusions of other studies carried out in women, namely, that no adverse psychological consequences seem to arise from genetic testing for BRCA1/2 mutation [21, 22]. This hypothesis may, with increasing clinical evidence, also be valid in male subjects.

This study has several limitations. Firstly, the small sample size does not allow an absolute generalization of the observed results. Secondly, the absence of short-term increase in anxiety and depression levels does not guarantee the absence of deterioration in long-term psychological conditions. Lastly, we believe that psychological evaluation in a genetic-testing setting is a complex topic, which should be carried out using diversified and numerous tools to grasp the facets of individual experiences.

Further investigations are clearly needed in order to deepen knowledge upon psychological implication of genetic testing in male suffering from and at high-risk for MBC. We intend to expand the experience of our center by implementing the use of quantitative methods with focus groups and with the involvement of family members in psychological support interviews.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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