Breast Cancer in Men

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Purpose: **Breast cancer in men is uncommon; 1500 new cases are diagnosed in the United States yearly. Optimal management of breast cancer in men is unknown because the rarity of the disease precludes large randomized trials. A review of the literature was undertaken with emphasis on articles published over a 10-year period.**

Data Sources: **Articles published between 1942 and 2000 on breast cancer in men were identified by using CancerLit, MEDLINE, and study bibliographies.**

Study Selection: **All retrospective series and studies focusing on the epidemiology, risk factors, genetics, and pathology of breast cancer in men.**

Data Extraction: **Data on the epidemiology, risk factors, genetics, pathology, molecular markers, prognostic factors, therapy, and outcomes of breast cancer in men.**

Data Synthesis: **Carcinoma of the male breast accounts for 0.8% of all breast cancers. Risk factors include testicular disease, benign breast conditions, age, Jewish ancestry, family history, and the Klinefelter syndrome. *BRCA2* mutations predispose men to breast cancer and may account for 4% to 14% of all cases. Pathology data were reviewed: 81% of tumors were estrogen receptor positive, 74% were progesterone receptor positive, 37% overexpressed c-erbB-2, 30% overexpressed p53, 79% overexpressed Bcl-2, 51% overexpressed cyclin D1, and 39% overexpressed epidermal growth factor receptor. Prognostic factors include tumor size, histologic grade, and lymph node status; survival is similar to that of breast cancer in women when patients are matched for age and stage. Adjuvant hormonal therapy and chemotherapy, using the same guidelines as for women, are recommended for men. Hormonal therapy is the primary therapy for metastatic disease; chemotherapy should be reserved for hormone-refractory disease.**

Conclusion: **Breast cancer is similar in men and women; however, breast cancer in men is more frequently hormone receptor positive and may be more sensitive to hormonal therapy.**

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Carcinoma of the male breast is a relatively rare disease that accounts for less than 1% of all cases of cancer in men. Because of the rarity of the disease, most information has been obtained from small, single-institution, retrospective studies or by extrapolation from breast cancer trials in women. We have previously reviewed the literature on breast cancer in men (1) and now present an update that focuses on the molecular and pathology data that has been published over the past decade.

Methods

We identified articles published between 1942 and 2000 on breast cancer in men using CancerLit, MEDLINE, and bibliographies from other publications. We reviewed all retrospective series and studies that focused on the epidemiology, risk factors, genetics, pathology, molecular markers, prognostic factors, therapy, and outcomes of breast cancer in men.

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Epidemiology and Risk Factors

In 2002, approximately 1500 new cases of male breast cancer will be diagnosed in the United States, and 400 men will die of this disease (2). In contrast to the increasing incidence of breast cancer in women, the incidence of breast cancer in men has remained stable over the past four decades (3). The median age at diagnosis is 68 years compared with 63 years in women (4); however, the disease has been reported in males ranging from 5 to 93 years of age (5). The bimodal age distribution seen in women is absent in men; the incidence increases exponentially with age (6). In most western countries, men account for approximately 1% of cases of breast cancer. In Tanzania, by contrast, 6% of cases of breast cancer are diagnosed in men (7), and in countries in central Africa, a substantially higher proportion of cases of male breast cancer have been reported (8). The reasons for this geographic variability remain unclear.

Many of the risk factors (**Table 1**) for breast cancer in men involve abnormalities in estrogen and androgen balance, which indicates that breast cancer in men, as in women, may be hormonally driven. An elevated risk has been seen in patients with undescended testes, congenital inguinal hernia, orchiectomy, orchitis, testicular injury, and infertility (8, 9). The Klinefelter syndrome, which is characterized by a 47,XXY karyotype, small testes, azospermia, and gynecomastia, is also a risk factor for breast cancer in men; affected men may have up to a 50-fold increased risk (10). Breast cancer in men may be a marker for the Klinefelter syndrome; between 4% and 20% of men with breast cancer have been unexpectedly found to have this syndrome, which affects only 0.1% of the general population (8, 10, 11). Other possible risk factors that relate to hormonal levels include obesity, which causes increased peripheral aromatization of estrogens, and cirrhosis, which results in a hyperestrogenic state (8, 9, 12, 13).

A family history of breast cancer in female relatives has also been shown to be an important predisposing factor. Data from the Surveillance, Epidemiology, and End Re-

Table 1. **Risk Factors for Breast Cancer in Men**

Testicular abnormalities
Undescended testes
Congenital inguinal hernia
Orchiectomy
Orchitis
Testicular injury
Infertility
Klinefelter syndrome
Positive family history
Benign breast conditions
Nipple discharge
Breast cysts
Breast trauma
Radiation exposure
Increasing age
Jewish ancestry

sults program of the National Cancer Institute showed that men with a positive family history have an odds ratio for developing breast cancer of 3.98 (14). The risk increases with increasing numbers of first-degree relatives affected and with young age at diagnosis in affected relatives. Benign breast conditions, such as nipple discharge, breast cysts, or history of breast trauma; radiation exposure; increasing age; and Jewish ancestry have also been associated with an increased risk for breast cancer in men (9). Gynecomastia probably does not represent a significant risk factor. Clinical gynecomastia has been reported in 6% to 38% of cases of breast cancer in men, which suggested that it could be a predisposing factor (15, 16). However, large reviews of gynecomastia in healthy men have found that 35% have clinical gynecomastia (17) and 40% have histologic evidence of gynecomastia (18). Thus, the rates in male patients with breast cancer do not seem to be higher than those in the general population.

GENETICS

Approximately 15% to 20% of male patients with breast cancer have a positive family history, although only 7% of the general male population has an affected family member (15, 19–22). Therefore, researchers have suspected that some families may carry genetic mutations that provide an increased risk for breast cancer. In women, the breast cancer susceptibility genes *BRCA1* and *BRCA2* are thought to account for most hereditary breast cancers. Mutations in these genes confer a 40% to 70% risk for developing breast cancer by age 70 years. In men, *BRCA1* does not appear to be associated with a significantly increased risk for breast cancer, although mutations in this gene have been described in affected men (23). However, men with *BRCA2* mutations are predisposed to breast cancer. This gene was first identified by Wooster, who localized it to 13q12-13 and described multiple cases of breast cancer in men that showed linkage to this area (24). Families in which breast cancer has occurred and at least one male has been affected have been reported to have a 60% to 76% chance of carrying *BRCA2* mutations (25, 26). Thus, the presence of breast cancer in men within a family with documented breast cancer indicates a high likelihood of a *BRCA2* mutation.

The frequency of *BRCA2* mutations in men without a strong family history is much lower. A population-based study from California found that only 2 of 54 cases (4%) had *BRCA2* mutations (21). Other series (**Table 2**) report that between 11% and 40% of men with breast cancer carry this mutation (27–32). The highest known prevalence of *BRCA2* mutations in male patients with breast cancer is in Iceland, where a founder mutation accounts for 40% of all cases (28). Little is known about the distinguishing characteristics of breast cancer in men with *BRCA2* mutations, although men with a mutation may present with disease at an earlier age (33).

PATHOLOGY

Almost all of the histologic subtypes of breast cancer that have been described in women have also been reported in men. Approximately 90% of all breast tumors in men are invasive carcinomas; the remaining 10% are noninvasive (34). The proportion of noninvasive cancers is higher than that seen in women before the introduction of mammography and may be due to the small size of the male breast, which simplifies the detection of small breast masses (34). Almost all of the noninvasive cancers are ductal carcinoma in situ. Lobular carcinoma in situ is extremely rare because of the absence of terminal lobules in the normal male breast; it has only been reported in conjunction with invasive lobular carcinoma (15, 35, 36). Ductal carcinoma in situ of the male breast differs from that of the female

Table 2. ***BRCA2* Mutations in Breast Cancer in Men**

Author, Year (Reference)	Patients Tested	Patients with *BRCA2* Mutations	Patients with *BRCA2* Mutations	Patients with Positive Family History
	n		%	
Couch et al., 1996 (27)	50	7	14	80
Thorlacius et al., 1996 (28)	30	12	40	25
Friedman et al., 1997 (21)	54	2	4	17
Mavraki et al., 1997 (29)	28	3	11	36
Haraldsson et al., 1998 (30)	34	7	21	13
Csokay et al., 1999 (31)	18	6	33	0
Díez et al., 2000 (32)	17	3	18	53

Table 3. **Pathologic Features of Breast Cancer in Men***

Pathologic Feature	Total	Tumors		References
		Positive or Immunoreactive	Positive or Immunoreactive	
	n	%		
Estrogen receptor	1301	1053	81	11, 15, 22, 34, 41–45, 48, 51–82
Progesterone receptor	1040	766	74	15, 22, 34, 43–45, 48, 51–69, 71–73
C-erbB-2†	511	190	37	48, 50, 58–61, 73, 76, 79, 83–88
p53 protein†	472	143	30	48, 57–61, 73, 76, 77, 83, 87, 89–92
bcl-2	193	153	79	60, 61, 83, 93
Cyclin D1	117	60	51	61, 94
EGFR	61	24	39	59, 75

* Data pooled from multiple studies; EGFR = epidermal growth factor receptor.
† Tested by immunohistochemistry.

breast in that almost 75% of cases are a papillary subtype and almost all cases are low to intermediate grade (37).

In men, the predominant histologic subtypes of invasive carcinoma are infiltrating ductal carcinoma, which accounts for more than 80% of all tumors (38–45), and papillary carcinoma, which makes up about 5% (22, 38, 39, 45–47). Lobular carcinoma is much less common in men than in women and represents only 1% of all cases (15, 22, 44). The rarer subtypes, such as medullary, tubular, mucinous, and squamous carcinomas, have all been reported in men, although they may be slightly more uncommon than in women (34, 43–45). Inflammatory carcinoma and Paget disease are seen with similar frequency in men and women (34, 45, 46).

Carcinomas of the male breast have a higher rate of hormone receptor positivity than do carcinomas of the female breast when matched for tumor stage, grade, and patient age (48–50). Our review of the literature indicates that 81% of breast cancers in men are estrogen receptor positive, and 74% are progesterone receptor positive (**Table 3**) (11, 15, 22, 34, 41–45, 48, 51–82). In contrast to women, men do not have a higher incidence of estrogen receptor–positive tumors with advancing age (34, 51, 60, 61).

Molecular Markers

C-erbB-2, p53, Bcl-2, cyclin D1, and epidermal growth factor receptor (EGFR) are important in the pathogenesis and prognosis of breast cancer in women. Recent literature has evaluated their role in carcinoma of the male breast, and we present a synthesis of these data (**Table 3**). The *c-erbB-2* protooncogene encodes for a transmembrane receptor of the tyrosine kinase family, which is closely related to EGFR. This protein is expressed in 20% to 30% of breast cancers in women and may be associated with a poor prognosis (95). Pooled data indicate that 37% of tumors overexpress c-erbB-2 as detected by immunohistochemistry (48, 50, 58–61, 73, 76, 79, 83–88). Although these data are the best available, they must be interpreted with caution because antibody preparations and the definitions for positive staining were not standardized and varied considerably among studies. Recently, Bloom and colleagues presented data on 58 male patients who were tested for c-erbB-2 overexpression (88). Twenty-six of these patients had been evaluated in an earlier study, and 35% were reported as overexpressing c-erbB-2 (79). When the same tumors were reevaluated by using stricter criteria to define positive immunohistochemistry staining, only one sample had either 2+ or 3+ staining. This study suggests that the older data may have been overestimating the rate of c-erbB-2 expression. Bloom and colleagues' study also evaluated the patient's tumors by using fluorescent in situ hybridization and found that none of the 58 tumors had gene amplification. This is the only study to date that has used fluorescent in situ hybridization to evaluate *c-erbB-2* gene amplification in breast cancer in men. The results suggest that breast cancer in men may have either low rates of c-erbB-2 expression or protein overexpression without gene amplification. It is unclear whether c-erbB-2 expression is a negative prognostic factor in breast cancer in men. Several small studies have associated c-erbB-2 expression with decreased overall survival (58, 79, 83), but the Mayo Clinic series of 76 men, which is the largest series to date, found no association between c-erbB-2 expression and overall survival (61).

P53 is a tumor suppressor gene that controls cell growth by inducing cell cycle blockade, apoptosis, and cell differentiation. *P53* gene alterations are the most common single genetic abnormality in breast cancer in women and are present in approximately 30% of cases (95, 96). When the *p53* gene is mutated, the abnormal protein accumulates within the cell and can be detected by immunohistochemistry. Several studies have evaluated the incidence of *p53* mutations in breast cancer in men. In our review of the literature, we found 472 cases of breast cancer in men that were tested for *p53* mutations using immunohistochemistry; 143 cases (30%) tested positive for a mutation (48, 57–61, 73, 76, 77, 83, 87, 89–92). These results are similar to data reported for breast cancer in women. The prognostic significance of *p53* mutations in breast cancer in men has not been clearly established, but most studies have

found *p53* mutations to be associated with decreased survival (55, 57–60, 87).

Bcl-2 is a protooncogene that inhibits apoptosis and thereby promotes cell growth. In breast cancer in women, expression of Bcl-2 has been associated with favorable prognostic features (97). Several studies have investigated the incidence of Bcl-2 expression in breast cancer in men. Overall, Bcl-2 expression was seen in 153 (79%) of 193 cases (60, 61, 83, 93). Men may have significantly higher rates of Bcl-2 expression than women (60), but Bcl-2 expression has not been shown to have prognostic significance in men (60, 61, 93). The high rates of expression of Bcl-2 in male breast cancer suggest that apoptotic mechanisms may be important in the etiology of breast cancer in men.

Cyclin D1 is involved in cell-cycle regulation and helps control the cell's entry into S phase. In breast cancer in women, this gene is oncogenic but appears to be associated with a favorable prognosis (95). A total of 117 tumors of the male breast were tested for cyclin D1 overexpression; 60 (51%) were immunoreactive (61, 94). This number is very similar to the 50% rate of overexpression seen in women (95). Rayson and colleagues (61) found that cyclin D1 negativity was associated with significantly decreased progression-free survival, indicating that gene overexpression may be a favorable prognostic factor in men with carcinoma of the breast.

The data on EGFR expression are even more limited. Epidermal growth factor receptor is a transmembrane glycoprotein that is present in low levels in normal breast tissue and is overexpressed in 35% to 60% of breast cancers in women (96). Overexpression of EGFR in women is inversely correlated with estrogen receptor expression and may be a negative prognostic factor. Only two studies have reported the rates of EGFR expression in men. Fox and colleagues (75) found that 16 of 21 cases (76%) expressed EGFR, and Willsher and colleagues (59) reported that 8 of 40 cases (20%) showed EGFR expression. No association was found with either estrogen receptor status or with prognosis, although conclusions are limited by very small sample size.

Prognostic Factors and Outcome

As in women, axillary lymph node status, tumor size, histologic grade, and hormone receptor status have been shown to be significant prognostic factors in men with breast cancer. Lymph node involvement is the most important negative prognostic factor for breast carcinoma in men (19, 45, 46, 65, 98). In a series of 335 patients, Guinee and colleagues (98) reported 5-year survival rates of 90% for histologically node-negative disease versus 65% for node-positive disease (98). They also found that the number of involved axillary lymph nodes was predictive of survival, even after adjusting for tumor size, skin involvement, and patient age. The 10-year survival rate for patients with histologically node-negative disease was 84% compared with 44% for one to three positive nodes, and 14% for four or more positive nodes.

Table 4. **Survival Rates for Breast Cancer in Men**

Variable	Survival Rate, %		References
	5-Year	10-Year	
Overall survival	36–66	17–52	11, 15, 19, 44, 45, 47, 100–103
Stage I	55–100	52–89	38, 41, 43, 103, 104
Stage II	41–78	10–52	38, 41, 43, 104
Stage III	16–57	2–23	11, 43, 104
Stage IV	0–14	0	11, 41, 102, 104
Node negative	57–100	43–84	15, 19, 38, 39, 64, 98, 105, 106
Node positive	31–60	11–35	15, 19, 38, 39, 64, 98, 105, 106
Disease-specific survival	52–74	26–51	19, 44, 45, 102, 103

Tumor size has also been shown to be a significant prognostic factor in breast cancer in men (16, 19, 22, 41, 98, 99). In a series of 397 patients in France, 5-year crude survival rates by tumor size were 85% for tumors measuring less than 2 cm in diameter, 63% for tumors 2 to 5 cm, and 51% for tumors greater than 5 cm (19). High histologic grade is similarly associated with decreased survival rates (43, 99, 100). Ribeiro and colleagues (43) found a statistically significant difference in 5-year survival based on histologic grade of tumor (grade 1, 76%; grade II, 66%; and grade III, 43%).

Finally, most evidence points to hormonal status in men being a prognostic factor, although the number and size of studies are limited. A study from Princess Margaret Hospital in Toronto, Ontario, Canada, of 229 patients found that estrogen receptor positivity predicted better overall survival in univariate analysis; but after adjustment for patient age, tumor size, lymph node status, and type of therapy, this difference was no longer significant (15). However, a large study of 215 patients from health care institutions in eastern Wisconsin showed that men with hormone receptor–positive tumors had improved overall survival, even after adjustment for tumor stage and axillary lymph node status (45).

Clinical outcome for men with breast cancer is similar to that for women. Five-year overall survival rates for all stages of breast cancer in men have been reported to range from 36% to 66%, and 10-year overall survival rates range from 17% to 52% (100, 101). Disease-specific survival rates are somewhat higher; 52% to 74% of patients are alive at 5 years and 26% to 51% are alive at 10 years (19, 102). Overall and disease-specific survival rates are shown in **Table 4**. Stage of disease predicts survival rates; overall 5-year survival rates are 55% to 100% for stage I, 41% to 78% for stage II, 16% to 57% for stage III, and 0% to 14% for stage IV disease (11, 38, 39, 41, 43–45, 104).

Although older articles have reported that men with breast cancer have poorer survival rates than women (46, 47), most recent series show that men and women have

Table 5. **Presenting Signs and Symptoms**

Presenting Signs and Symptoms	Frequency, %	References
Breast mass	50–97	15, 16, 19, 43, 44, 103, 104, 107
Nipple retraction	10–51	15, 19, 44, 104
Local pain	4–20	15, 44, 104, 107
Nipple ulceration	4–17	15, 44, 103, 107
Nipple bleeding	2–9	15, 103, 107
Nipple discharge	1–12	15, 16, 19, 44, 103, 104, 107
None	1–2	15, 107

equivalent prognoses when matched for age and stage of disease (19, 48, 60, 101). Men do have lower overall survival rates, but this is probably due to later stage at presentation, more advanced age, and high rates of death from intercurrent illness. The large study done in France of 397 male patients with breast cancer found that 40% of patients died of intercurrent illness (19). Other studies have corroborated this finding (45, 67). The cause of these high death rates in men with breast cancer remains unclear; however, it may in part be due to the older age of these men at presentation.

Clinical Features

Approximately 85% of men with breast cancer present with a painless subareolar mass (43). Other common presenting signs and symptoms are nipple retraction, local pain, nipple ulceration, nipple discharge, and nipple bleeding (Table 5). Most patients present with more than one sign or symptom (15, 44). The rate of nipple involvement has been reported to be approximately 40% to 50%, perhaps because of the sparsity of breast tissue and the central location of most tumors (58, 105). The disease has a slight predilection for the left breast (16, 44, 45, 107) with a left-to-right ratio of 1.07:1 (5). Bilateral disease is rare. Men are more likely than women to have a delay between the onset of symptoms and a diagnosis of breast cancer, possibly because of the limited public awareness of breast cancer in men. This delay in diagnosis may contribute to men presenting at later stages than do women.

When a man presents with a breast mass, the primary differential diagnosis is gynecomastia versus carcinoma. Mammography can be useful in distinguishing a benign from malignant condition; carcinoma is often eccentric with irregular, spiculated margins (1). Screening mammography has no role in men because of the rarity of the disease and the small size of the male breast, which allows easy palpation of most masses. As in women, a biopsy of any suspicious mass should be performed. Fine-needle aspiration has been evaluated in male patients and has been found to be very sensitive and specific (108). When malignancy is diagnosed, men should have the same staging evaluation as women. The American Joint Committee on Cancer (AJCC) classification is the most widely used staging system and is based on tumor size, presence of nodal metastases, and presence of distant metastases (TNM) (109). Tissue evaluation should include determining tumor grade and hormone receptor status because both have prognostic significance. An algorithm for diagnostic and treatment recommendations is shown in the **Figure**.

Local Therapy

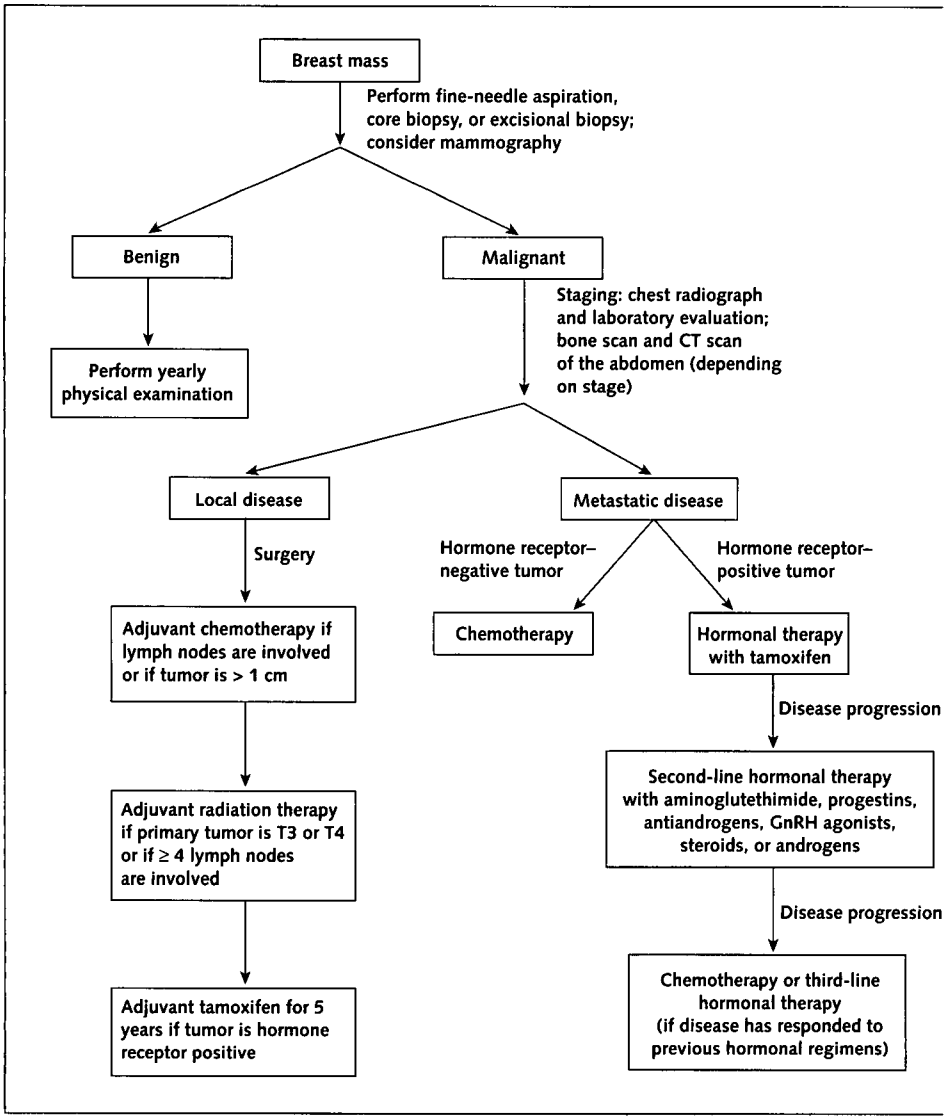
For men who present with nonmetastatic disease, the currently recommended surgical therapy is modified radical mastectomy. Historically, most men were treated with radical mastectomy; however, because women have been shown to do as well with a more limited surgical approach, most men are also now treated with modified radical mastectomies. Studies that have compared radical with modified radical mastectomy in men have found equivalent local recurrence and survival rates for these two surgical approaches (41, 71, 110). Thus, it seems reasonable to recommend less extensive surgery. Because the male breast has sparse amounts of tissue, segmental mastectomy probably does not have a role in the treatment of carcinoma of the male breast. As in women, axillary dissection is an essential part of surgical therapy (16, 19).

Limited data are available for determining which patients need radiation therapy after modified radical mastectomy. Several studies have found that radiation reduces the risk for local recurrence but does not change overall survival (19, 40, 45, 104). Some authors have suggested that the central location of tumors in the male breast may predispose to internal mammary lymph node metastases. They conclude that radiation to the internal mammary nodes should be considered for all patients and that chest wall radiation should be considered for patients with locally advanced disease (111).

Adjuvant Therapy

Adjuvant hormonal therapy with tamoxifen in women with estrogen receptor–positive breast carcinoma has resulted in significantly improved survival rates. Because men have high rates of hormone receptor positivity, adjuvant hormonal therapy is theoretically very promising. No randomized clinical trials have evaluated the use of adjuvant tamoxifen. Several large studies have retrospectively compared men who were treated with tamoxifen in an adjuvant setting with men who received no hormonal therapy and have found improved survival in patients treated with tamoxifen (15, 43, 63). Ribeiro and Swindell (63) compared 39 patients with stage II and stage III disease who received tamoxifen with historical controls and found a 5-year survival of 61% versus 44%, suggesting a significant benefit from tamoxifen (63). The studies of adjuvant tamoxifen may underestimate its benefit because most men were treated for less than 2 years. The optimal length of therapy in women is 5 years; therefore, a greater benefit in men may been seen with longer duration of therapy. Based on the available data, we recommend that all men with hor-

Figure. **Treatment recommendations for breast cancer in men.**



CT = computed tomography; GnRH = gonadotropin-releasing hormone.

mone receptor–positive tumors be treated with tamoxifen for 5 years.

The role for adjuvant chemotherapy in men is less established, but the limited data do suggest a benefit. Given the considerable toxicity of chemotherapy, few men with early-stage disease have received chemotherapy; thus, even retrospective data have been difficult to obtain. The National Cancer Institute studied 24 male patients who were given adjuvant chemotherapy for node-positive stage II breast cancer (69). The 5-year survival rate among treated patients was 80%, which was significantly better than the survival rates among historical controls. The experience with adjuvant anthracycline therapy was reviewed at M.D. Anderson Cancer Center (70). Eleven node-positive patients who were treated with adjuvant chemotherapy (10 with an anthracycline-based regimen) were found to have an estimated 5-year survival rate of greater than 85%, which was substantially better than survival rates of historical controls. Other authors have also found improved outcomes in patients treated with adjuvant chemotherapy (16, 42, 45). With most data supporting a benefit of adjuvant chemotherapy in men and the clear benefit for adjuvant chemotherapy in women, we would offer adjuvant chemotherapy to men who have substantial risk for recurrence. Because there are no data with which to determine exactly which men will benefit from adjuvant chemotherapy, we use the same guidelines in men as in women and offer chemotherapy to men with node-positive disease or primary tumors that are larger than 1 cm.

Therapy for Metastatic Disease

Hormonal therapy has been the mainstay of treatment for metastatic carcinoma of the male breast for the past 5

decades. Initial hormonal therapies were ablative orchiectomy, adrenalectomy, and hypophysectomy. Farrow and Adair (112) described the first response to orchiectomy in 1942, and orchiectomy became the standard of care for treatment of metastatic disease. Jaiyesimi and colleagues reviewed ablative therapies in 447 patients and found response rates of 55% for orchiectomy, 80% for adrenalectomy, and 56% for hypophysectomy (1). Patients who responded to orchiectomy were more likely to respond to second-line ablative therapies, and responding patients had improved survival (113).

Additive hormonal therapy has also been shown to have substantial response rates in metastatic breast carcinoma in men. It is an appealing alternative to ablative therapies because such therapy is reversible, avoids surgical morbidity and mortality, and is psychologically more acceptable to most men than orchiectomy. Overall rates of response to the various additive therapies have been reported as 75% for androgens, 57% for antiandrogens, 50% for steroids, 32% for estrogens, 50% for progestins, 40% for aminoglutethimide, and 49% for tamoxifen (1). These numbers may be optimistic because responders are more likely to have been reported in the literature. Estrogen receptor positivity appears to predict response to hormonal therapy. Jaiyesimi and colleagues found that 69% of 35 men with estrogen receptor–positive tumors responded to hormonal manipulation compared with 0% of 8 men with estrogen receptor–negative tumors (1). We recommend tamoxifen as first-line hormonal therapy because of its established efficacy in men and limited toxicity. In addition, most oncologists have considerable experience with this drug in women.

Systemic chemotherapy, which is another option for men with metastatic breast cancer, is usually reserved for second-line therapy because most men will respond to hormonal manipulation. One study directly compared chemotherapy with hormonal therapy and found superior response rates in patients treated with hormonal therapy (114). Chemotherapy, however, can offer significant palliation to men in whom hormonal therapy has failed or those with hormone receptor–negative disease. Response rates reported in the literature are 67% for 5-fluorouracil, doxorubicin, and cyclophosphamide; 55% for doxorubicin and vincristine; 53% for cyclophosphamide; 33% for cyclophosphamide, methotrexate, and 5-fluorouracil; and 13% for 5-fluorouracil (1). For all other regimens or single agents, fewer than five cases have been reported in the literature. For all chemotherapy regimens, the overall response rate was 40% (1).

CONCLUSIONS

Carcinoma of the male breast has many similarities to breast cancer in women, but the diseases have different genetic and pathologic features. Both *BRCA1* and *BRCA2* mutations can cause breast cancer in women, but only *BRCA2* mutations confer a significant risk to men. Noninvasive carcinomas in men are all low- to intermediate-grade ductal carcinoma in situ; pure lobular carcinoma in situ is extremely rare. Most invasive carcinomas are infiltrating ductal, with lobular carcinoma representing only about 1% of invasive disease. Men have higher rates of estrogen and progesterone positivity than do women but similar percentages of c-erbB-2, p53, cyclin D1, and EGFR overexpression. Men may be more likely to have tumors that overexpress bcl-2, but the clinical significance of this finding is not clear.

The diagnostic evaluation and staging of breast cancer in men is similar to that in women. For localized disease, modified radical mastectomy is the preferred surgical approach. There is no evidence that adjuvant radiation therapy after mastectomy improves survival, although men may have a higher risk for internal mammary lymph node metastases and in theory could benefit from internal mammary radiation therapy. Although the evidence is limited, most studies point to a benefit from both adjuvant tamoxifen and chemotherapy. Given the known benefit of adjuvant therapy in women, we recommend that men also be offered adjuvant therapy using the same guidelines that are the standard of care for women. Metastatic disease can be treated with either hormonal therapy or chemotherapy. Because men have high rates of response to additive hormonal therapy, this approach is recommended for first-line treatment in hormone receptor–positive disease. Tamoxifen is the most accepted front-line additive therapy. Selective aromatase inhibitors (anastrozole and letrozole) have been approved for first-line treatment of metastatic breast cancer in women, but there are no published reports of responses in men. Chemotherapy can be of use for hormone-refractory disease.

Areas for future investigation are plentiful. Larger studies of pathologic markers would be helpful to define which genetic abnormalities play a role in breast cancer in men and to determine which markers are important prognostic factors. The role of adjuvant hormonal and chemotherapy deserves further study, especially to determine which subgroups of men will benefit. New hormonal and chemotherapeutic agents, such as selective aromatase inhibitors and taxanes, deserve investigation for the therapy of carcinoma of the male breast. Finally, men should be strongly encouraged to participate in clinical trials so that prospectively gathered information will be available and more can be learned about breast cancer in men.

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