Review Article
Article de revue

Male breast carcinoma

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Objective: To review the epidemiology, presentation, diagnosis, molecular genetics, treatment and prognosis of male breast cancer. **Data sources:** Articles, written in English or French, selected from the Medline database (1966 to January 2001), corresponding to the key words "male breast cancer," according to the following criteria: covering institutional experience or comparing diagnostic and treatment modalities, and epidemiologic or general reviews. **Study selection:** Of 198 articles found 50 fulfilled the review criteria. **Data synthesis:** Risk factors included advanced age, a positive family history, Jewish origin, black race, excess exposure to female hormones (Klinefelter's syndrome), environmental exposure (irradiation), alcohol, obesity, higher socioeconomic or higher educational status and childlessness. Gynecomastia remains a controversial factor, this term being used for both a histologic reality and a physical finding. Advanced disease is characterized by pain, bloody discharge and skin ulceration. There is no definitive diagnostic algorithm. Experience with male breast mammography is limited, and imaging is less informative for patients under 50 years of age. Fine-needle aspiration tends to overestimate the rate of malignancy. The commonest histologic finding is infiltrating ductal adenocarcinoma. Treatment includes modified radical mastectomy, followed by cyclophosphamide–methotrexate–5-fluorouracil or 5-fluorouracil–Adriamycin–cyclophosphamide chemotherapy for disease of stage II or greater. Radiotherapy does not seem to add any benefit. The disease is highly receptor-positive; however, many patients discontinue tamoxifen due to side effects. The most important prognostic factors are tumour size, lymphatic invasion and axillary node status. **Conclusions:** Because of the low incidence of male breast cancer, advances will be obtained mainly with the rapid transfer of newly gained knowledge in female mammary neoplasia. The increased use of adjuvant chemotherapy combined with tamoxifen postoperatively may have a positive impact on survival. Public education should be oriented toward men at higher risk to reduce the interval between appearance of symptoms and consultation. Rigorous data collection will allow for thorough reporting of risk factors and thus the possibility of characterizing the etiology of this disease.

Objectif : Examiner l'épidémiologie, la présentation, le diagnostic, la génétique moléculaire, le traitement et le pronostic du cancer du sein chez l'homme. **Sources des données :** Des articles, en anglais ou en français, choisis dans la base de données Medline (1966 à janvier 2001), à l'aide des mots clés «male breast cancer», selon les critères suivants : études de l'expérience en établissement ou comparaison de méthodes de diagnostic et de traitement et études épidémiologiques ou générales. **Sélection d'études :** Au nombre des 198 articles trouvés, 50 satisfaisaient aux critères d'examen. **Synthèse des données :** Les facteurs de risque comprenaient l'âge avancé, les antécédents familiaux positifs, l'appartenance à la descendance juive ou à la race noire, l'exposition excessive aux hormones féminines (syndrome de Klinefelter), l'exposition à des rayonnements dans l'environnement, la consommation d'alcool, l'obésité, un statut socio-économique favorisé ou un niveau d'instruction élevé et l'infécondité. La gynécomastie demeure un facteur prêtant à controverse, car cette expression est utilisée pour désigner tant une réalité histologique qu'une constatation physique. Au stade avancé, ce cancer est caractérisé par de la douleur, un écoulement sanguinolent et de l'ulcération cutanée.Il n'y a pas d'algorithme diagnostique bien déterminé. L'expérience de la mammographie chez l'homme est limitée et l'imagerie pratiquée chez les patients de moins de 50 ans apporte moins d'information. L'aspiration à l'aiguille fine entraîne généralement une surestimation de la malignité. Le carcinome canalaire infiltrant est la constatation histologique la plus courante. Le traitement fait appel à la mastectomie radicale modifiée, suivie d'une chimiothérapie associant la cyclophosphamide, le méthotrexate et le 5-fluoro-uracile ou le 5-fluoro-uracile, l'Adri-

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amycin et la cyclophosphamide dans les cas de cancer de stade II ou supérieur. La radiothérapie ne semble pas apporter un avantage supplémentaire. Dans la grande majorité des cas, les récepteurs de la tumeur sont positifs, mais bon nombre de patients arrêtent de prendre du tamoxifène à cause des effets secondaires. La taille de la tumeur, l'envahissement du système lymphatique et l'atteinte des ganglions axillaires sont les facteurs de pronostic les plus importants. **Conclusions :** En raison de la faible incidence de cancer du sein chez l'homme, les progrès dans ce domaine reposeront principalement sur la transposition rapide des connaissances nouvelles de la néoplasie mammaire chez la femme.La plus grande utilisation, après la chirurgie, de la chimiothérapie adjuvante associée au tamoxifène pourrait avoir un effet positif sur la survie. L'éducation du public devrait cibler les hommes à risque plus élevé afin d'écourter l'intervalle entre l'apparition des symptômes et la consultation. La collecte rigoureuse de données permettra un compte rendu détaillé des facteurs de risque et, par conséquent, la caractérisation de l'étiologie de ce cancer.

Male breast cancer remains a rare entity, accounting for less than 1% of cases of mammary neoplasia,[1] which explains our lack of knowledge about this condition. Much of what we know and what we do about male breast cancer comes from our knowledge of breast cancer in women. This article offers an overview of the disease, focusing particularly on its epidemiology and risk factors, clinical presentation, radiologic and histologic diagnosis, treatment and prognosis. A segment on its molecular genetics is also included.

Methodology

All articles from 1966 to January 2001, corresponding to the key words "male breast cancer" were retrieved from the Medline database. From these 198 papers, 50 were selected with the following criteria: articles written in English or French, articles relating institutional experience with a substantial number of cases, articles comparing diagnostic or treatment modalities, epidemiologic reviews and general reviews.

Epidemiologic and risk factors

A multitude of risk factors have been advanced for male breast cancer, many of which remain to be proven.

Age[1–11]

In North America and Western Europe, male breast cancer is a disease of older people, with a peak incidence around 60 years of age, 10 years later than its female counterpart.

A family history of breast cancer[1,12–17]

A family history is a definite risk factor: 5% to 30% of male breast cancer patients report a family history of the disease. The significance of paternal or maternal cancer, as well as the number of affected relatives is less definite. The role of genetic testing for *BRCA1* and *BRCA2* and other molecular genetic markers is important in this respect.

Ethnicity and race

Male breast cancer is more prevalent in Ashkenazi Jews.[1,9,18,19] North American studies mention a higher incidence in African-Americans.[12] Whether this is solely due to genetic factors or to issues of social inequity that may cause certain risk factors to be more prevalent in that community remains to be found. For example, obesity, considered to be a risk factor, seems more common within this segment of the American population. Interestingly, according to a study in sub-Saharan Africa, male breast cancer makes up a larger proportion of all breast cancers than in the West, ranging from 4% to 13%.[6]

Exposure to female hormones

In 1995, Ganly and Taylor[20] reported on a patient in whom breast cancer developed after 14 years of hormone replacement therapy prescribed after a sex change operation. A similar case was reported by Pritchard and colleagues.[21]

Cirrhosis is associated with a hyperestrogenic state and therefore increases the risk of breast cancer. Hormonal changes in cirrhosis are quite similar to those in Klinefelter's syndrom. According to Misra and colleagues,[22] the incidence of breast cancer in cirrhotic men would be higher if these patients survived long enough.

In Klinefelter's syndrome, the plasma estradiol level is elevated, the testosterone level is decreased, levels of luteinizing hormone and follicle-stimulating hormone are high and infertility and gynecomastia are characteristic. Men with Klinefelter's syndrome are at 20 times higher risk for breast cancer than normal men. Similar hormonal imbalances are seen in other cases of testicular dysfunction such as orchitis or undescended testes.[12,18–25]

Environmental exposure

Soap and perfume workers may be at higher risk.[25] We hypothesize that this occurs through abnormal aromatization of steroid molecules. Similarly, furnace and steel workers are also at a higher risk, possibly through the accumulation of minute damage at the genetic level induced by carbon and its derivatives.[19,26] The importance of heat or electromagnetic fields has not been clearly established yet,[23] although an increased risk has been noted.[27] A history of chest-wall irradiation predisposes to breast cancer.[2,27–30]

Social history and habitus

In the context of alcohol-induced cirrhosis, alcohol increases the risk of breast cancer.[9] There is contradiction among different authors as to the importance of cigarettes. Obesity is associated with increased estrogen levels through peripheral aromatization, and thus constitutes a risk factor.

Gynecomastia

Gynecomastia as a risk factor is subject to debate, since the term has been used both for a histologic and for a physical finding. Many consider it a risk factor because histologic gynecomastia is a sign of feminization, associated with excess estrogen and decreased testosterone levels. It is characterized by hyperplasia of ductal and stromal elements and manifests clinically as a soft, mobile, tender mass in the retroareolar region. Gynecomastia may indicate physiologic changes (senescence, puberty), hormonal imbalances (Klinefelter's syndrome, hypogonadism), systemic disease (cirrhosis, chronic renal insufficiency), neoplastic transformation (adrenal carcinoma, pituitary adenoma, hepatocellular carcinoma), the effects of drugs (cimetidine, marijuana, thiazide diuretics, omeprazole, tricyclic antidepressants, spironolactone, diazepam, anabolic steroids, exogenous estrogen) and idiopathic changes.

Childlessness

Men with no children are reported to be at a 5 times higher risk than fathers, according to D'Avanzo and La Vecchia.[1] An underlying infertility problem is noted in many cases, reinforcing the importance of hormonal imbalance in the pathogenesis of the disease.[9]

High socioeconomic status, higher education

More educated men and men from higher social classes tend to be at a greater risk for breast cancer. Multiple factors may explain this. First, men from lower social classes have a shorter life expectancy, and thus may be underrepresented, because they do not reach the age groups at which breast cancer is more prevalent. Second, the patterns by which men seek medical advice vary among different social classes. Finally, those who pursue higher education tend to put off having children.[1,18]

Clinical features

The majority of patients present with a painless, firm, subareolar lump.[2,3,7,8,33–35] At the intermediate stage, the lump may be painful to touch and may be accompanied by clinical gynecomastia[2,3,9] and nipple retraction.[2,3,7,8,33] Advanced disease is characterized by spontaneous pain or tenderness,[2,9,33] a bloody nipple discharge,[2,3,7,9,33,34] skin ulceration and Paget's disease.[2,3,9,33,35,36] The mass is centrally located 70% to 90% of the time.[33] It may infrequently be located in the outer external quadrant.[34] Its mean diameter varies, ranging from 2.0–3.5 cm.[7,33] There may be fixation to skin or muscle[3,33] and axillary adenopathy.[2,33] The disease has a slight predilection for the left breast. Bilateral cancers are reported in up to 5% of cases. The presence of gynecomastia and its reporting in the literature is highly variable, probably due to the nonspecificity of the term. Bone pain and cough may indicate distal metastasis. Second primary cancers are present in 5% to 15% of men and correspond to neoplastic disease patterns expected in the male population: prostate, gastrointestinal tract, lung and skin.[33]

Pathological features[2,9,11,33,37]

All histologic types of breast cancer have been identified in men, the most common type being infiltrating ductal adenocarcinoma (70%–95% of cases). Ductal carcinoma in situ is infrequent. Klinefelter's syndrome is associated with lobular carcinoma. The rate of receptor positivity is high, up to 85% (higher than in females).

Diagnosis[5,9,12,27,33,38–40]

The work-up of breast masses in men involves a large differential diagnosis, including the following: cancer, gynecomastia (histologic finding), abscess, hematoma, lipoma, fat necrosis, ductal ectasia, intraductal papilloma, sarcoma, cysts and metastatic disease. All unilateral breast lumps in men aged 40 years or older deserve investigation. Up to 30% of middle-aged men and 60% of men in their seventh decade have benign histologic gynecomastia. In 95% of cases, bilateral gynecomastia found on physical examination is associated with nonmalignant states. Elements of high suspicion for cancer thus include painless, nontender, hard masses, subareolar but eccentric to the nipple, masses fixed to the pectoral fascia and skin changes. A variety of diagnostic tools complete the history and examination.

With respect to mammography,[27,32,41] the normal male mammogram demonstrates lucent fat with a few strands of ductal or connective tissue extending from the nipple. Cancer is characterized by a well-defined mass, subareolar but eccentric to the nipple, with spiculated margins, frequently lobulated and accentuated by architectural distortion. Microcalcifications are uncommon. When present, they tend to be large, round and scattered, not grouped. Gynecomastia is described as a triangular or round mass of increased density, with flame-shaped margins, bilateral and symmetric in the retroareolar region. The density blends gradually into the surrounding fat. Lipomas are characterized by a thin capsule that surrounds radiolucent lipomatous tissue. Fat necrosis may be hard to differentiate from cancer, but usually there is a positive history of trauma. Ultrasonography can provide information as to the descriptive aspects of the lesion but has

no net advantage over mammography and is therefore rarely used. Ductography can occasionally be useful to highlight abnormal intraductal lesions when there is nipple discharge but no palpable mass.

According to most authors,[3,12,33,34,39] fine-needle aspiration cytology (FNAC) is an appropriate means of taking samples. Some suggest that a surgical or core biopsy of all suspicious lesions should be done. The approach seems to depend on hospital practice and experience.

The algorithm for an accurate, cost-efficient and painless diagnosis of male breast cancer remains to be defined. Practice diverges from that of female breast cancer because of the paucity of mammary tissue in the male breast and the rarity of the disease. In terms of imaging, experience in male breast mammography is limited. According to Vetto and colleagues,[39] mammograms are of no benefit for patients younger than 50 years. They reported a high rate of false-positive results due to gynecomastia and epidermal cysts. As for the histologic diagnosis, these authors found that FNAC has a tendency to overcall malignancy, due to epithelial hyperplasia. In another

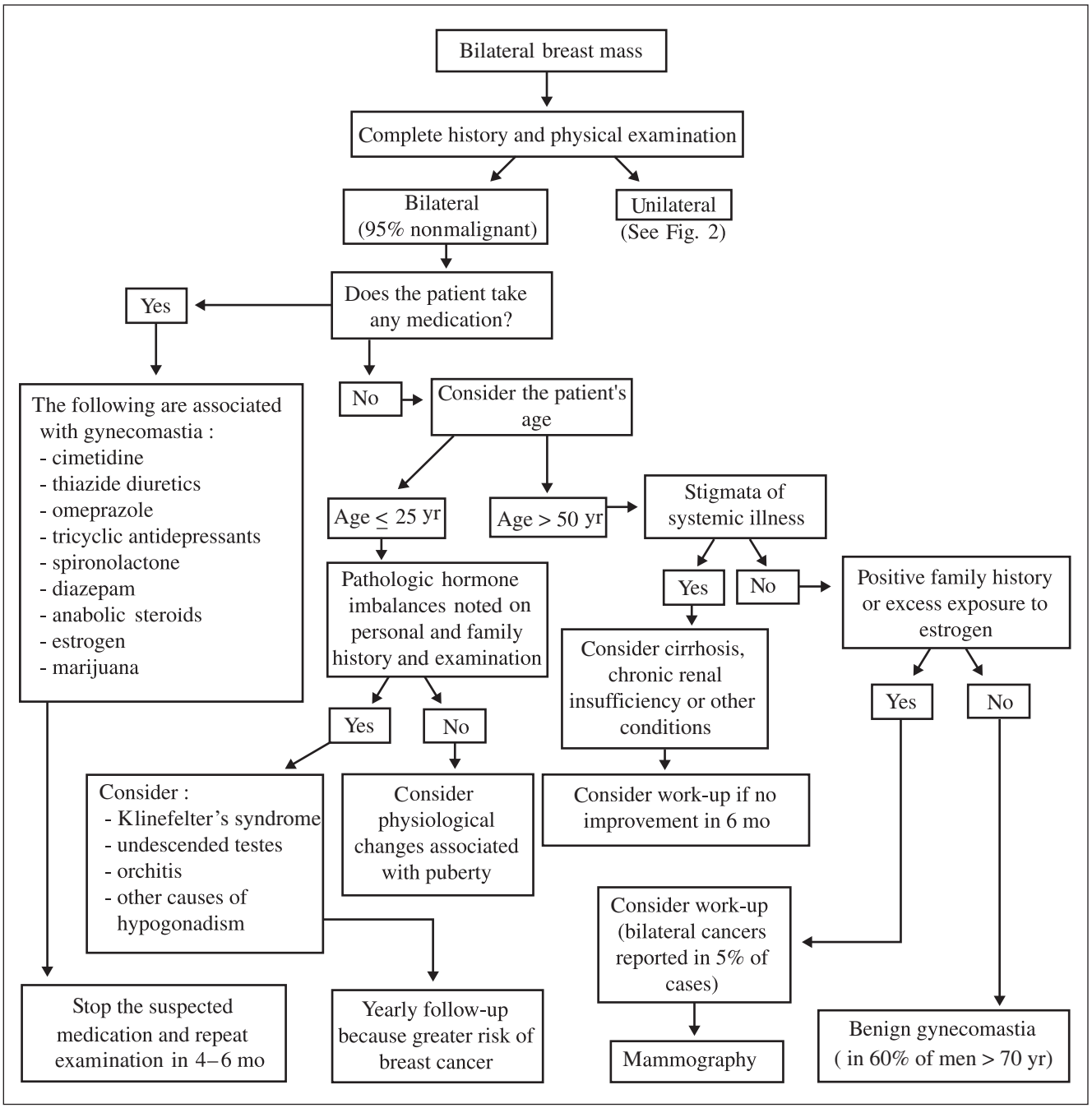

FIG. 1. Suggested algorithm for the work-up of a bilateral breast mass in men.

study, Volpe and colleagues[12] tried to document the actual differences in the diagnostic work-up between gynecomastia and breast cancer. They claimed that both mammography and FNAC have considerable value in differentiating gynecomastia from cancer but that mammography is not indicated for patients under the age of 50 years and in cases of central, painful, nonindurated masses.[12] In a review of the mammographic appearance of male breast disease, Applebaum and associates[32] concluded that a location distal from the nipple may be the most useful, but nondefinitive finding to suggest a benign lesion. We propose the work-up algorithms presented in Figs. 1 and 2.

Molecular genetics: an overview

Studies have shown the signifi-

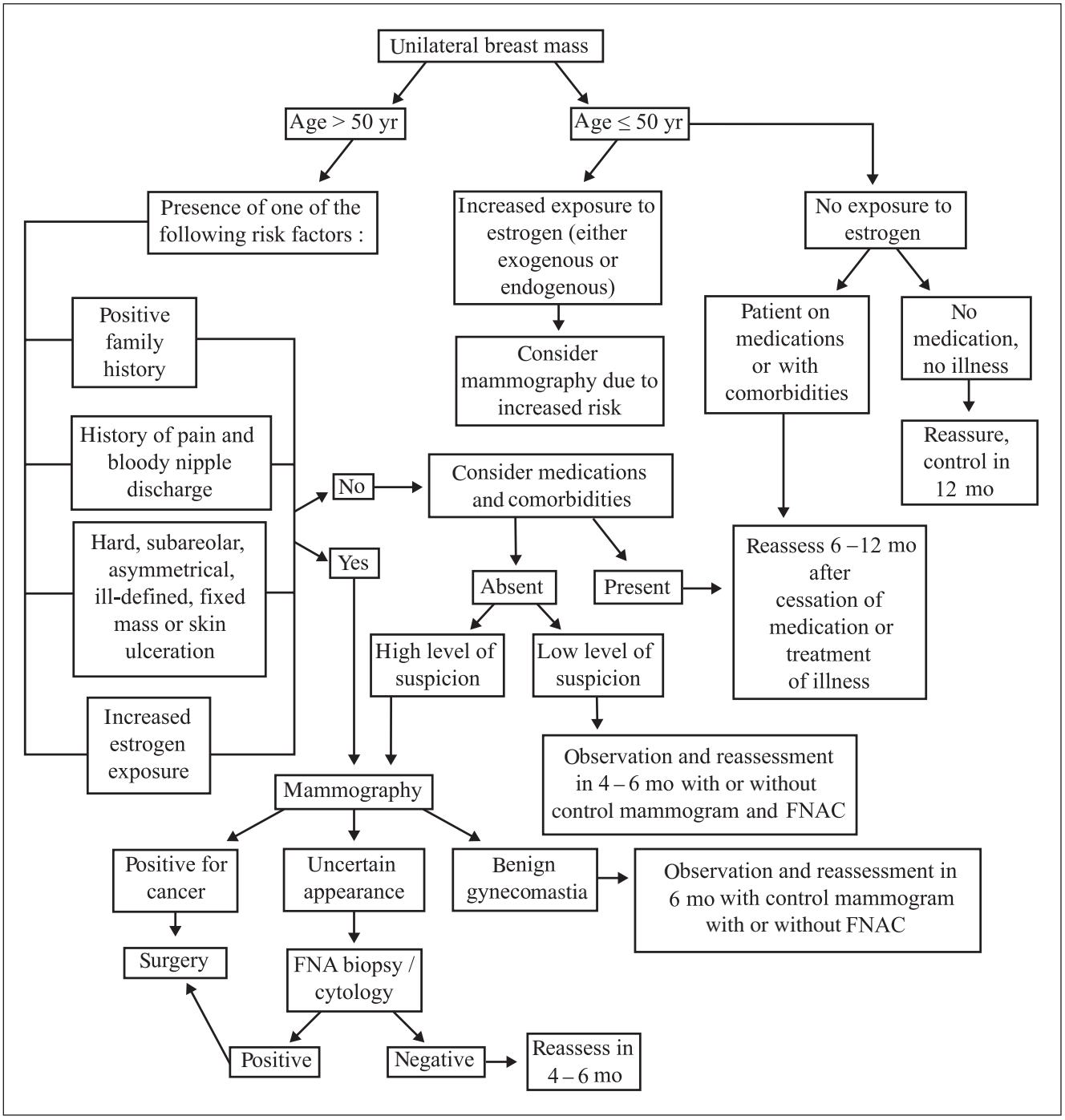

FIG. 2. Suggested algorithm for the work-up of a unilateral breast mass in men. FNA = fine-needle aspiration, FNAC = fine-needle aspiration cytology.

cance of mutations in the *BRCA2* gene located on chromosome 13q 12–13 in male breast cancer.[10,25,42] Csokay and associates[37] state that up to 40% of men with breast cancer carry the mutated gene. This number must be taken with some reserve as it applies to a study of men drawn only from Hungary. According to Mavraki and colleagues,[43] 7% to 11% of male breast cancer patients have *BRCA2* mutations. Another study from Iceland showed that 12% of patients were carriers of this mutation.[44] One study has shown that underexpression of cyclin D1 is associated with a faster progression of the disease. This information seems to contradict standard knowledge.[24] Other molecular markers include *bcl-2*, an apoptosis inhibitor, and *MIB-1*, a factor involved in proliferative activity. Both have high levels of expression in aggressive cancers. Overexpression of mutated *p53* gene is also involved in the evolution of male breast cancer.[45,46] Finally, *erb2* is also expressed in male breast cancer.[47,48]

Treatment

Most authors prefer modified radical mastectomy for surgical excision of these cancers, and some suggest simple mastectomy followed by adjuvant modalities.[3,5,9,33,34]

Various rates of use of radiotherapy have been reported. Most papers have indicated no net overall survival benefit of radiotherapy.[3,5,8–10,18,40] There is contradiction as to its advantages in preventing local recurrence; both presence and absence of benefit are reported.[3,28,33] There is a clear indication for radiotherapy when it is impossible to lift the entire tumour burden from the axilla.[18]

Systemic chemotherapy should be administered to patients with stage II or greater disease.[4] The most used regimens are CMF (cyclophosphamide–methotrexate–5-fluouracil), FAC (5-fluorouracil–Adriamycin–cyclophosphamide) and other anthracyclin-based regimens.[4,9,33] Its role in node-negative disease remains to be clarified.[4,8] Regional administration of chemotherapy has been described.[49]

Hormonal manipulations constitute an essential part of adjuvant therapy, since male breast cancers have a high rate of hormon-receptor positivity. In the past, orchiectomy, adrenalectomy and even hypophysectomy have been practised. Today, tamoxifen is the standard hormonal treatment.[4,5,9,33] Tamoxifen increases the 5-year disease-free survival rate of patients with stage II cancer.[9] Side-effects of the treatment include hair loss, skin rash, impotence, decrease in libido, weight gain, hot flashes, mood changes, depression and insomnia. It should be noted that a recent study suggested an incidence of side-effects of 62.5%. In the study of Donegan and Redlich,[33] up to 21% of patients subsequently discontinued Tamoxifen within a year. Node-positive disease should be treated by surgery and a combination of chemotherapy and tamoxifen.

Evidently, there is no standardized protocol. Goss and associates[11] showed that age, lymph-node status, tumour size, presence or absence of metastatic disease at diagnosis and decade of diagnosis influenced the choice of primary treatment modality. Patients were more likely to be treated with chemotherapy if they had positive lymph nodes or if they were younger. Patients were more likely to receive hormonal therapy if they had large tumours or a positive family history. For disease recurrence, hormonal manipulations with radiotherapy, or chemotherapy with radiotherapy can be administered for palliative purposes.

Prognostic factors

The 3 most important prognostic factors are tumour size, lymphatic invasion and axillary node status.[2,3,9,33,34] Unfortunately, nodal involvement is present in up to 60% of patients.[7] Other factors for a poor prognosis include negative receptor status, p53 protein accumulation and high histologic and nuclear grades.[7] Histologically, pure mucinous, medullary, papillary and tubular carcinomas are associated with a more favourable prognosis.[33] Finally, delayed diagnosis is a modifiable factor of negative outcome.[5,34] According to one study, time from the appearance of symptoms to the first physician contact was more than 6 months.[11] When all factors are taken into account, the overall 5-year survival is 85% for patients with node-negative status and 57% for patients with node-positive status,[9] with an average 5-year disease-free interval of 55%.[3] When prognostic factors, disease stage and age are matched, male and female breast cancers are associated with similar outcomes.[2,8] Poor prognosis is associated with a high rate of metastasis, the most common sites being bone, lung, brain, liver, pericardium, adrenal glands and pleura.[7]

Conclusions

Much knowledge remains to be gained about male breast cancer. Considering the relatively low incidence of this disease, advances will be registered with the rapid transfer of newly gained knowledge in female breast cancer. As such, a recently published case report promotes sentinel lymph-node scintidetection and biopsy in men.[50] The increased use of adjuvant chemotherapy combined with tamoxifen (or improved derivates) after surgery may have a positive impact on survival. As for prevention, some public education should be oriented toward men at higher risk to reduce the time between appearance of symptoms and consultation. Finally, rigorous data collection allows for thorough reporting of risk factors and thus the possibility of characterizing the etiology of this disease.

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