Radiodiagnostics in the Follow-Up of Breast Cancer Patients

Max Dieterich · Bernd Gerber

Universitäts-Frauenklinik am Klinikum Südstadt, Rostock, Germany

Key Words

Breast cancer: recurrence, metastasis, follow-up · Bone scan, hot spot · X-ray, chest

Summary

Background: New treatment options have revived discussions about the role of perioperative screening and intensive follow-up in early breast cancer (BC), with the role of radiological staging in follow-up for BC patients being a controversial subject. The aim of this literature review is to determine the importance of X-ray in BC patients. **Material and Methods:** Literature research was performed in Pubmed. A total of 173 abstracts were reviewed, and 27 original articles and 1 Cochrane Database System Review were evaluated. **Results:** Perioperative staging and routine staging for follow-up in asymptomatic patients has no benefit for disease free survival and overall survival, and is associated with a high false positive rate. Hot spots in bone scans are mostly of benign origin and require further X-ray clarification. **Conclusion:** Due to the currently unproven benefit and missing therapeutically consequences, X-ray can not be recommended for perioperative screening or regular follow-up in asymptomatic BC patients.

Schlüsselwörter

Brustkrebs: Rezidiv, Metastasen, Nachsorge · Skelettszintigraphie, Hot Spot · Thorax-Röntgen

Zusammenfassung

Hintergrund: Bedingt durch neue Therapieoptionen gibt es derzeit erneut Diskussionen über die Rolle des perioperativen Screenings und regelmäßiger Nachsorgeuntersuchungen bei Brustkrebspatientinnen. Hierbei wird die Rolle von Röntgenuntersuchungen kontrovers diskutiert. Ziel dieser Übersichtsarbeit ist es, den Stellenwert des Röntgen von Brustkrebspatienten perioperativ und in der Nachsorge zu bestimmen. **Material und Methoden:** Eine Literaturrecherche wurde in Pubmed vorgenommen. Insgesamt wurden 173 Abstracts begutachtet und 27 Originalarbeiten sowie ein Cochrane Database System Review ausgewertet. **Ergebnisse:** Röntgenuntersuchungen zum perioperativen Staging sowie in der routinemäßigen Nachsorge asymptomatischer Patienten ergeben keinen Benefit für das erkrankungsfreie Intervall und das Gesamtüberleben, und sind mit einer hohen Falsch-Positiv-Rate verbunden. «Hot Spots» in der Skelettszintigraphie sind meist benignen Genese und bedürfen häufig weitererführender radiologischer Abklärung ohne Benefit für das Outcome. **Schlussfolgerung:** Aufgrund des (bisher) nicht nachgewiesenen Benefits und fehlender therapeutischer Konsequenzen sind Röntgenuntersuchungen weder perioperativ noch in der Nachsorge von asymptomatischen Patientinnen indiziert.

Introduction

Currently, there are new public discussions regarding perioperative screening and intensive follow-up of asymptomatic breast cancer (BC) survivors [1, 2]. This is explained by newer

treatment options. It is supposed that an early detection and earlier treatment of recurrence would improve the outcome, especially the overall survival (OAS). For the detection of clinically occult metastases, different imaging methods are available, however, most of them are very expensive and not

Table 1. Perioperative staging in breast cancer patients without clinical signs of tumor spread; bone and pulmonary metastases detected by chest X-ray only

Author, year [reference]	Patients, n	Patient characteristics	Overall distant metastasis, %	Bone metastasis, %	Pulmonary metastasis, %	Conclusion
Abuzallouf, 2007 [34]	785	retrospective stage ^a I+II stage III	0.7 16.2	3.7	0.8	no routine perioperative staging
Puglisi, 2005 [7]	516	prospective stage I–III stage I+II stage III	6.4	6.3 14.0	0.9 7.2	staging only in stage III patients
Ravaioli, 2002 [5]	1,218	retrospective pT1–4, N0/1/2	3.8	3.1	0.7	staging only in high risk patients (T3 or N>3+)
Myers, 2001 [6]	1,307 (bone) / 3,884 (pulmonary)	retrospective stage I stage I stage III	– – –	6.8 8.8 24.5	0.1 0.2 1.7	staging only in high risk patients (T3 or N>3+)
Gerber, 2003 [11]	1,076	retrospective T1–4, N1–3 pT1c pT 2 pT 3 N0 N1–3+ N ≥ 4+	2.8 1.6 3.0 15.1 1.9 4.0 8.5	0.9 0.9	1.8 0.9 0.9	perioperative screening is not warranted in T1–2 and / or N0–3+; false positive findings
Ravaioli, 1998 [35]	406	prospective T1–4, pN0–2	5.7	4.4	1.5	staging is needed in high risk groups (T4 N>4+) only
Lee, 2005 [36]	1,939	retrospective stage I–III stage I stage IIA stage IIB stage IIIA stage IIIB stage IIIC	1.4 0.7 0.6 0.6 4.0 16.7 4.4	0.2	0.7	bone scan is of little value in stage I–II, but highly recommended in stage III or higher
Ciatto, 1985 [37]	1,017	prospective stage I–II stage III	0.26 2.77	0.59 (overall detection rate)	0.29 (overall detection rate)	no routine perioperative staging

^aAJCC stage.

widely available. X-ray is an established method in the detection of pulmonary and bone metastases, it is cheap and always available. The aim of the presented literature review is the evaluation of X-ray in the detection of pulmonary and bone metastases in patients without signs of distant tumor spread (cM0) at the time of primary treatment (perioperative staging) and during follow-up of asymptomatic BC survivors, and its role in the further diagnosis of suspicious hot spots in bone scans (BS).

Materials and Methods

PubMed was searched for articles (clinical trials, meta-analyses, randomized controlled trials, and reviews) which studied the impact of BS and X-

ray in the detection rate of metastases in symptomatic and asymptomatic BC patients, perioperatively and during normal follow-up.

Key words used for the search were: bone scan, chest X-ray (CXR), X-ray, metastasis, detection rate, breast cancer follow-up, breast cancer, breast, recurrence, hot spot. In total, 173 abstracts were examined in MEDLINE. From these, 27 abstracts and 1 Cochrane database system review thoroughly met the objective. These articles were obtained and reviewed.

Results

Perioperative Screening

With regard to perioperative staging examinations, several studies have conformingly shown that there is no general advantage for low risk BC patients in the detection of distant

Table 2. Regular chest X-ray during follow-up in asymptomatic breast cancer survivors

Author, year	Patients, n	Patient characteristics	Asymptomatic metastases	False positive results	DFS	OAS	Conclusion
Hurria et al., 2003 [15]	533	retrospective, stage I–II breast cancer	0.8%	90%	–	–	chest imaging is of limited value in asymptomatic patients
Imoto and Jitsuiki, 1998 [18]	550	retrospective, stage I–III	1.5%	–	–	no benefit	intensive follow-up should be limited to high-risk patients only
Pivot et al., 2000 [13]	1125	prospective, p1–4 pN0/+ cM0	10.3%	–	no benefit	no benefit	reduce follow-up to careful history
Yeh et al., 1995 [16]	316	retrospective, pT1–2 pN0/+ cM0	2%	89.0%	–	–	high false positive rate.
Rosselli Del Turco et al., 1994 [14]	1243	randomized, pT1–4 pN0/+ cM0, intensive vs. clinical group	9.0 vs. 5.7%	–	benefit in clinical group	no benefit	diagnostic tests only in the presence of symptoms
GIVIO, 1994 [17]	1320	prospective, T1–3, N0–1, cM0, intensive vs. clinical group	31 and 21% of primarily detected metastases	–	no benefit	no benefit	routine use of intensive follow-up should be discouraged
Joseph et al., 1998 [12]	1898	retrospective, pT1–4 pN0/+ cM0, intensive vs. PE group	6.8% overall metastases: 21 vs. 79%	–	–	no benefit	diagnostic tests only in symptomatic patients

DFS = Disease-free survival; OAS = overall survival.

metastasis, as well as for disease free survival (DFS) and OAS (table 1). This is also true for the detection of pulmonary or bone metastases by CXR. Dillman et al. [3] have shown a distant metastases rate in stage I BC patients of 0.4%, in stage IIa of 1.2%, and in stage IIb of 6.8%, and recommend staging only in high risk patients with tumors greater than pT3 or with positive lymph node involvement. For the BC stages, the TNM system and the definition of the American Joint Committee on Cancer (AJCC) were used [4]. A different definition of high risk patients has been established by Ravaioli et al. [5]. According to them, BC patients can be divided into 2 different risk groups: a low risk group containing pT1–3 patients with up to 3 involved lymph nodes, and a high risk group including all patients with more than 3 involved lymph nodes, pT4, and pN2 tumors. Other studies like Myers et al. [6], Puglisi et al. [7], and Samant et al. [8] defined similar groups of high and low risk BC patients. Perioperative detection rates for pulmonary and bone metastases are very low in low risk BC patients and are incommensurate with the high costs of staging examinations [9, 10]. In addition to high rate of false positive findings and missing therapeutic consequences, perioperative staging examinations let the patients feel even more insecure and decrease their health-related quality of life [11]. Most authors (table 1) recommended perioperative screening in high risk patients only. However, even in these patients, there is no apparent advantage in the early

detection of occult metastases. The only reason for screening these patients is the avoidance of aggressive adjuvant treatment in cases of distant metastases [11]. It is not adequate to define risk profile by tumor size and number of involved lymph nodes. The individual risk is better defined by biological characteristics like endocrine responsiveness, HER2 expression, and epidermal growth factor receptor (EGFR).

Chest X-Ray during Follow-Up of BC Patients

Most studies concerned with regular CXR in follow-up of asymptomatic BC patients were published years ago (table 2). All major studies have shown an insignificant detection rate of distant metastasis and no benefit for OAS [12–14]. Again, CXR screening is associated with little clinical value, high false positive rates, and high costs [15, 16]. Early detection simply increases the period during which a metastasis is observed and does not add a survival advantage in asymptomatic patients [12–14, 17, 18]. Any treatment option in the situation of asymptomatic metastasis results in a decrease of quality of life. Offering CXR only to symptomatic patients during follow-up, makes a significant difference in the time to detection of metastasis in asymptomatic patients without enlarging the risk of increased OAS [14]. Especially in asymptomatic patients, early detection of metastases would initiate treatment and can easily lead to overtreatment. Up to now, there is no evidence that early detection of advanced disease and imme-

Table 3. Chest X-ray in symptomatic breast cancer survivors and influence on outcome

Author, year	Patients, n	Patient characteristics	Detection rate, %	False positive rate, %	DFS	OAS	Conclusion
Pivot, 2000 [13]	1,125	randomized pT1–4 pN0/+ cM0	10.3 (by imaging)	–	no benefit	no benefit	no routine CXR for follow-up
Kokko, 2003 [27]	472	randomized pT1–4 pN0/+ cM0 regular CXR vs. clinically	3.7 vs. 3.5	80 vs. 78	no benefit	no benefit	no routine CXR for follow-up
Ciatto, 1983 [26]	1,697	retrospective symptomatic vs. asymptomatic	39 vs. 7		no benefit	no benefit for follow-up	no routine CXR

DFS = Disease-free survival; OAS = overall survival; CXR = chest X-ray.

Table 4. Chest X-ray for further evaluation of hot spot in bone scan in breast cancer survivors pT1–4 pN0/+ cM0

Author, year	Patients, n	Patient characteristics	Detection rate, %	Conclusion
Kara, 2003 [28]	75	retrospective 1 solitary hot spot on a bone scan	26.1 (bone metastases); 73.1 (benign origin); 0.8 (unclear etiology)	solitary rib lesions on bone scans are frequently of benign origin
Chen, 2003 [33]	115	retrospective 1 hot spot 2 hot spots 1 hot spot + concurrent bone abnormality	14.3 11.1 81.8	regular follow-up for 2 years after detection of rib lesions is recommended
Wups, 2002 [29]	199	retrospective solitary rib hot spots	11.8 (bone metastases, 9.1 with pain); 88.2 (benign origin)	further radiodiagnostics are needed for clarification
Jacobson, 1990 [31]	301	retrospective 1 hot spot (asymptomatic patients) 2 hot spots (asymptomatic patients)	11 24	most solitary rib hot spots are benign
Koizumi, 2003 [38]	5,538	retrospective solitary or multiple lesions	12.7 (overall detection rate); 41 (solitary metastases); 59 (multiple metastases)	solitary hot spots are independent prognostic factors
Baxter, 1995 [32]	34	retrospective reliability of bone scan interpretation	41 (malignant); 35 (benign); 24 (indeterminate)	further radiodiagnostics are needed for clarification
Jacobson, 1990 [31]	183	retrospective reliability of bone scan interpretation	9.3 (malignant)	further radiodiagnostics are needed for clarification
Tumeh, 1985 [39]	2,851	retrospective 1 hot spot	9.8 (solitary malignant); 53.2 (benign fractures); 27 (associated with postoperative radiation therapy)	solitary rib lesions are most frequently associated with a benign etiology

diate treatment would improve OAS. To the knowledge of the authors, there are no ongoing or planned studies dealing with this question. Not only overtreatment but also the simple knowledge of metastases in asymptomatic patients can result in decreased health-related quality of life. On the other hand, there is a high demand on follow-up in BC patients. Especially young women with sometimes more aggressive tumors are not

willing to reduce the frequency of follow-up visits in order to be reassured about their health status. Good strategies of sharing information between patient and doctor might help women to be equally reassured when less follow-up is offered and might resolve this conflict. Regular physical examinations and yearly mammography alone are as effective as more intensive approaches based on laboratory tests and instrumental

tests [19]. As a result, less intensive follow-up strategies based on periodical clinical examinations seem as efficient as more intense surveillance schemes in low risk asymptomatic patients. High false positive rates and lacking therapeutically options are also limitations to intensive follow-up in this patient group. According to literature reviews, a regular follow-up could only be recommended in high risk patients. However, all guidelines [20–23] do not recommend regular diagnostic follow-up particularly in this high risk group. So far, there are no data showing any OAS benefit of early treatment in clinically asymptomatic patients. A study published by John et al. [24] even indicates an increased risk of BC, particularly in genetically susceptible women, who underwent some form of low-dose radiation like CXR. Taking this into consideration, CXR should be used even more restrictedly. Reduced follow-up strategies for BC can improve quality of life by reducing the anxiety experienced at each follow-up visit [25].

Chest X-Ray in Symptomatic BC Patients

Regarding the observations of John et al. [24], one has to also review the usefulness and frequency of CXR in symptomatic patients. The detection rate in symptomatic patients is generally higher than in asymptomatic patients but has no influence on DFS and OAS (table 3) [13, 26]. Whether recurrence was found at the scheduled follow-up visits or between scheduled visits, symptoms were the primary indicator of relapse. Within this symptomatic group, Pivot et al. [13] detected only 10.3% metastases by CXR, indicating a low importance of CXR in symptomatic patients. Approximately 3 times more CXR have to be taken to detect metastases in asymptomatic patients. In addition, it is associated with a high false positive rate [27]. Patients in whom relapse has been falsely suspected are likely to suffer anxiety and derive harm rather than benefit from the X-ray examination.

Chest X-Ray for Further Evaluation of Hot Spots in BC Survivors

BS is accepted as a very sensitive method for the investigation of skeletal metastases, and, despite rapid advances in all imaging modalities, there has been no serious challenge to BS for the detection of skeletal metastasis. Nevertheless, BS should

only be considered in symptomatic patients. Table 4 reviews the studies dealing with further evaluation of hot spots in BS. For further evaluation of pathological findings in BS, CXR is still an established procedure. The detection of solitary rib lesion either during perioperative staging or follow-up examinations in BC patients is not uncommon and presents a major diagnostic problem. Single hot spots in a BS are frequently of benign origin and cause a lot of unnecessary radiographic tests and expenses for the health system [16, 28, 29]. The more abnormalities occur in BS, the higher the risk of metastasis [30]. In asymptomatic patients with 1 or 2 abnormalities, most benign changes either remain unchanged or resolve within 12–24 month [31]. For further clarification of these mostly benign hot spots, additional CXR and other radiological tests are necessary [31, 32]. In cancer patients with 1 or 2 new BS abnormalities, correlative radiographs showing a benign abnormality are reliable [31]. Chen et al. [33] showed that direct tumor invasion to the chest wall or skin, 10 or more involved lymph nodes, and no radiotherapy were associated with increased risk of bone metastases whereas a longer time interval between surgery and rib lesion detection and longer persistence of the rib lesions were associated with lower risk of distant metastasis.

Conclusion

With the evidence presented in the synopsis above and the reviewed literature, the following conclusions can be drawn. For low risk BC patients, perioperative X-ray is not indicated. This also applies to routine X-ray and other radiological tests during follow-up in asymptomatic patients, due to no benefit in DFS, OAS, and high costs. A high number of false positive findings with further diagnostic procedures impair the quality of life. Hot spots in BS have to be carefully evaluated. In most cases, they are of benign cause, and the validity of these findings has to be assessed carefully. Due to lacking therapeutic potential, early detection is only valuable if more effective treatment modalities are available, and randomized clinical trials have shown their superiority in asymptomatic detected metastases compared to symptomatic patients.

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