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Chapter 2

Limited evidence base for locoregional treatment of patients aged 75 years or older with early stage breast cancer

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*Under review*
Abstract

Background
Treatment guidelines are merely based on randomized clinical trials, which are considered the evidence base for treatment of breast cancer. However, relatively few elderly are included in these trials. Therefore, the aim of this study was to quantify and qualify the evidence base for locoregional treatment of older women with early stage breast cancer.

Methods
The 66 randomized clinical trials on locoregional trials included in the national breast cancer guidelines comprise the evidence for locoregional treatment. Eligibility criteria of these trials were applied to a population-based cohort of elderly breast cancer patients. The population-based cohort consisted of 2,662 patients aged ≥65 years at diagnosis of early stage breast cancer, who were diagnosed between 1997 and 2004 in the geographically defined Comprehensive Cancer Center Region West, in The Netherlands. For all patients we calculated the proportion of the randomized clinical trials from which they would be excluded due to eligibility criteria. Based on this proportion, the evidence base was deemed 1) present, 2) partial, or 3) limited; corresponding with exclusion from less than 30%; 30-60%; or more than 60% of the trials, respectively.

Results
In patients aged 65-75 years, the evidence base was dependent on the number of comorbidities and whether patients had a previous malignancy. Contrary, the evidence base was limited for all patients aged 75 years or older; patients were excluded from more than 60% of the trials solely due to age. Overall, the evidence base for locoregional treatment was present for 35%, partial for 19%, and limited for 56% of elderly patients with early stage breast cancer.

Conclusions
The evidence base for locoregional treatment is limited for the majority of elderly breast cancer patients, and for all patients aged 75 years or older in particular.
Introduction

Up to 40% of breast cancer patients is 65 years or older at diagnosis. As breast cancer incidence increases with increasing age, changing demographics and continuously increasing life expectancy will further enlarge the number of elderly women confronted with breast cancer. Recently it was shown that in postmenopausal patients, breast cancer mortality increased with increasing age. Moreover, the risk of a distant recurrence in breast cancer patients aged 75 years or older was higher than in younger postmenopausal patients, which may be attributed to undertreatment of elderly patients.

The term undertreatment suggests less than optimal treatment. However, for elderly women with breast cancer it is largely unknown what optimal treatment is. The evidence base for treatment is mostly composed of randomized clinical trials. Despite comprising a large proportion of all breast cancer patients, elderly patients are underrepresented in these trials because of physician factors, patients factors, but also due to exclusion criteria. Moreover, exclusion criteria may hamper participation of a certain type of elderly patients in particular. Consequently, trial results may not necessarily be extrapolated to all elderly breast cancer patients.

In early stage disease, the evidence for adjuvant chemotherapy is mostly based on the Early Breast Cancer Trialist’s Collaborative Group meta-analyses. It is known that few women older than 70 years of age, and very few older than 80 were randomized into the studies included in these meta-analyses, and therefore the evidence base for chemotherapy in elderly breast cancer patients is rather limited. It is also known that elderly breast cancer patients are relatively often included in clinical trials on adjuvant endocrine therapy. However, there are few data on the evidence base for locoregional treatment in elderly patients with early stage breast cancer.

Therefore, the aim of this study was to quantify and qualify the evidence base for locoregional treatment of elderly patients with early stage breast cancer.

Methods

Early stage breast cancer includes patients with T0–T2 N0–N1 M0 breast cancer according to the seventh edition of the tumor node metastasis (TNM) classification. Locoregional treatment includes breast surgery, axillary surgery and postoperative radiotherapy.

The evidence base for locoregional treatment of early stage breast cancer patients was defined as all randomized clinical trials on locoregional treatment which are included in the national breast cancer guidelines. We chose to define the evidence base on the basis of the national breast cancer guidelines rather than on a systemic search strategy of the literature.
to better meet the aim of the study; all randomized clinical trials which translate to clinical
treatment decisions are incorporated in the guidelines. It was previously shown that national
treatment recommendations in different countries exhibited a large degree of congruency\textsuperscript{13}. Therefore, we used the Dutch guideline recommendations. In 2002, initiated by the Dutch
Institute of Health Care Improvement CBO and the Dutch National Breast Cancer Society,
the first national multidisciplinary guideline ‘Breast Cancer Treatment’ was implemented
in the Netherlands\textsuperscript{14}. Regular revisions ensure updated information and recommendations.
For this study, the most recent Dutch national guidelines were used (February 2012)\textsuperscript{14}. An
overview of recommendations for locoregional treatment of early stage breast cancer, and the
corresponding randomized clinical trials are shown in Supplementary tables 1 and 2.

The search engines Pubmed and Medline were used to retrieve the original articles. In case of a
systematic review or a meta-analysis of multiple randomized clinical trials, all individual trials
were retrieved and included. In case a study was used more than once, e.g. in more than one
recommendation or in two meta-analyses, it was included in the analyses only once.

We then examined the inclusion and exclusion criteria of each of the randomized clinical trials.
In case the authors referred to previous publications for extensive eligibility criteria, these
publications were retrieved. Previously, van Spall and colleagues defined reasons for excluding
individuals from a randomized clinical trial as poorly or strongly justified\textsuperscript{15}. Exclusion criteria
were defined to be poorly justified when based on, among others; age, physical ability or
disability, or a chronic health condition. Consequently, eligibility criteria in the current study
were categorized into three groups; 1) age, 2) a previous malignancy, and 3) comorbid disease.
All criteria were reported as exclusion criteria\textsuperscript{15}.

Finally, we compared the exclusion criteria with a population-based cohort of breast cancer
patients aged 65 years and older (FOCUS cohort), to see what proportion of patients would
have been disqualified for the trials. Thereby we aimed to quantify and qualify the evidence
base for locoregional treatment. The population-based FOCUS cohort (Female breast cancer
in the elderly: Optimizing Clinical guidelines USing clinico-pathological & molecular data)
comprises all consecutive incident breast cancer patients aged 65 years or older, who were
diagnosed in the geographically defined Comprehensive Cancer Center Region West in
The Netherlands, between 1997 and 2004. Information on patient characteristics, tumor
characteristics, treatment, follow up and outcome were recorded for all patients. Comorbidity
was categorized by the 10th edition of the International Statistical Classification of Diseases
and Related Health Problems (ICD-10)\textsuperscript{16}.

Statistical analyses
First, we calculated the frequency of all exclusion criteria. Second, we calculated what
proportion of elderly patients from the population-based FOCUS cohort would have been
disqualified for the trials, based on the exclusion criteria. There is no standard definition or cut-off whether there is an evidence base for treatment. Therefore we propose a qualification based on the proportion of randomized clinical trials, i.e. the evidence base, from which patients are excluded. The evidence base was deemed present in patients who are excluded from less than 30% of the trials, i.e. in patients who could have been included in at least 70% of the trials; partial in patients who are excluded from 30-60% of the trials; and limited in patients who are excluded from more than 60% of the trials. In patients for which an evidence base is deemed present, we conclude that guideline recommendations, which are based on these trials, can be extrapolated. To further qualify the evidence base, we evaluated which patients are excluded in particular. Patients were categorized based on age (65-75 years; ≥75 years)\textsuperscript{17}, the number of comorbitities they had (0-1; 2-4; ≥5 comorbitities) and whether they had a previous malignancy.

Results

Population-based cohort

Overall, 2,662 patients with early stage breast cancer were included in the current study. Mean age was 75.7 years (standard deviation 7.3 years); 1,319 patients were 75 years or older at diagnosis (49.5%). Patient and tumor characteristics are shown in Table 1. The number of comorbit diseases varied from 0 up to 11; most patients had 0 or 1 comorbid disease. The most prevalent comorbitities were circulatory (e.g. heart failure, hypertension), endocrine (e.g. diabetes mellitus, hypothyroidism) and musculoskeletal comorbitities (e.g. arthrosis, osteoporosis). The majority of the patients had stage II disease (n=1,532 (58%)).

Evidence base

The evidence base for locoregional treatment comprised 181 studies, among which six meta-analyses of 152 studies\textsuperscript{18-23}. Overall, 40 studies were excluded because there was no report of the study methods (e.g. the results were presented at a conference or at a meeting only) or the study was not a randomized clinical trial. After elimination of duplicates, the evidence base for locoregional treatment was composed of 66 unique randomized clinical trials.

Eligibility criteria

Adequate breast surgery or surgery with curative intent was required for participation in all clinical trials. As shown in Table 2, eligibility criteria on age, a previous malignancy and comorbid disease were defined in 67% (44/66); 58% (38/66) and 55% (36/66) of the randomized clinical trials, respectively. In case eligibility criteria on age were defined, patients aged 70 years and older were excluded in particular. Presence of comorbid disease was defined loosely in the majority of the trials, e.g. as ‘a medical condition contra-indicating therapy, adherence or follow-up’. Therefore, consensus based definitions of comorbid disease (WW, EB) were used for further analyses. These are included in Table 2.
Quantification and qualification of the evidence base

To quantify the evidence base, we calculated what proportion of elderly patients from the population-based FOCUS cohort would have been disqualified for the trials, based on the exclusion criteria. On average, elderly breast cancer patients were excluded from 52% (34/66, range 6% - 89%) of the randomized clinical trials which comprise the evidence base for locoregional treatment. Exclusion was evaluated for different groups of elderly patients, based on age, the number of comorbidities, and whether patients had a previous malignancy (Table 3). Overall, the evidence base for locoregional treatment was present for 35%, partial for 19%,

<table>
<thead>
<tr>
<th>Table 1. Characteristics of the population-based cohort of elderly patients with early stage breast cancer (n=2,662).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous malignancy</td>
</tr>
<tr>
<td>Any</td>
</tr>
<tr>
<td>Excluding NMSC</td>
</tr>
<tr>
<td>Excluding BCC</td>
</tr>
<tr>
<td>Number of comorbidities</td>
</tr>
<tr>
<td>0-1</td>
</tr>
<tr>
<td>2-4</td>
</tr>
<tr>
<td>≥5</td>
</tr>
<tr>
<td>Type of comorbidity (presence)</td>
</tr>
<tr>
<td>Circulatory</td>
</tr>
<tr>
<td>Respiratory</td>
</tr>
<tr>
<td>Endocrine</td>
</tr>
<tr>
<td>Neurologic</td>
</tr>
<tr>
<td>Psychiatric</td>
</tr>
<tr>
<td>Digestive</td>
</tr>
<tr>
<td>Musculoskeletal</td>
</tr>
<tr>
<td>T stage</td>
</tr>
<tr>
<td>T0</td>
</tr>
<tr>
<td>T1</td>
</tr>
<tr>
<td>T2</td>
</tr>
<tr>
<td>T3</td>
</tr>
<tr>
<td>N stage</td>
</tr>
<tr>
<td>Negative</td>
</tr>
<tr>
<td>Positive</td>
</tr>
<tr>
<td>Hormone receptor status</td>
</tr>
<tr>
<td>Positive</td>
</tr>
<tr>
<td>Negative</td>
</tr>
<tr>
<td>Unknown</td>
</tr>
<tr>
<td>Histological subtype</td>
</tr>
<tr>
<td>Ductal</td>
</tr>
<tr>
<td>Lobular</td>
</tr>
<tr>
<td>Unknown</td>
</tr>
</tbody>
</table>

SD: standard deviation; NMSC: non melanoma skin cancer; BCC: basal cell carcinoma

Quantification and qualification of the evidence base

To quantify the evidence base, we calculated what proportion of elderly patients from the population-based FOCUS cohort would have been disqualified for the trials, based on the exclusion criteria. On average, elderly breast cancer patients were excluded from 52% (34/66, range 6% - 89%) of the randomized clinical trials which comprise the evidence base for locoregional treatment. Exclusion was evaluated for different groups of elderly patients, based on age, the number of comorbidities, and whether patients had a previous malignancy (Table 3). Overall, the evidence base for locoregional treatment was present for 35%, partial for 19%,
Table 2. Frequency of exclusion criteria of 66 randomized clinical trials comprising the evidence base for locoregional treatment.

<table>
<thead>
<tr>
<th>Exclusion criteria on age (defined in 44/66 trials)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40 years</td>
<td>2</td>
</tr>
<tr>
<td>&lt;50 years</td>
<td>1</td>
</tr>
<tr>
<td>&lt;70 years</td>
<td>1</td>
</tr>
<tr>
<td>&gt;65 years</td>
<td>1</td>
</tr>
<tr>
<td>&gt;69 years</td>
<td>1</td>
</tr>
<tr>
<td>&gt;70 years</td>
<td>27</td>
</tr>
<tr>
<td>&gt;75 years</td>
<td>8</td>
</tr>
<tr>
<td>&gt;80 years</td>
<td>2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exclusion criteria on a previous malignancy (defined in 38/66 trials)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>20</td>
</tr>
<tr>
<td>Excluding BCC</td>
<td>13</td>
</tr>
<tr>
<td>Excluding NMSC</td>
<td>5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exclusion criteria on comorbid disease (defined in 36/66 trials)*</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECOG performance status &gt;2</td>
<td>6</td>
</tr>
<tr>
<td>ECOG performance status &gt;1</td>
<td>4</td>
</tr>
<tr>
<td>Renal disorders</td>
<td>5</td>
</tr>
<tr>
<td>Hepatic disorders</td>
<td>4</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>4</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>10</td>
</tr>
<tr>
<td>Hematological disorders</td>
<td>7</td>
</tr>
<tr>
<td>Non-malignant systemic disease</td>
<td>5</td>
</tr>
<tr>
<td>Serious non-malignant systemic disease</td>
<td>5</td>
</tr>
<tr>
<td>Medical condition contra-indicating therapy, adherence or FU</td>
<td>18</td>
</tr>
</tbody>
</table>

BCC: basal cell carcinoma; NMSC: non melanoma skin cancer; ECOG: Eastern Cooperative Oncology Group; FU: follow-up. *Adds up to more than 36 because multiple criteria may apply. ECOG performance status >2: survival after diagnosis less than 6 months; psychiatric disorder. ECOG performance status >1: nursing home at time of diagnosis; survival after diagnosis <6 months; psychiatric disorder. Renal disorders: creatinin >1.5 ULN. Hepatic disorders: ASAT >1.5 ULN; ALAT >1.5 ULN. Cardiac disorders: myocardial infarction; heart failure plus one of the following disorders; valve disorder, conduction disorder, arrhythmia, peripheral arterial obstructive disease or cerebrovascular accident; three or more of the following conditions; heart failure, cerebrovascular accident, arrhythmia, valve disorder, conduction disorder, venous disease, thrombosis, hypertension. Psychiatric disorders: depression; severe psychiatric disorder; dementia. Hematological disorders: thrombocytes <1.5 ULN; leukocytes >1.5 ULN; hemoglobin <1.5 ULN. Non-malignant systemic disease: diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (ICD10-III); endocrine, nutritional and metabolic diseases (ICD10-IV); diseases of the musculoskeletal system and connective tissue (ICD10-XIII); hypertension; peripheral arterial obstructive disease; kidney failure. Serious non-malignant systemic disease: survival after diagnosis less than 6 months; psychiatric disorder. Medical condition contra-indicating therapy, adherence or FU: survival after diagnosis less than 6 months; psychiatric disorder.
and limited for 56% of elderly patients aged 65 years or older with early stage breast cancer. In patients aged 65-75 years, the evidence base was dependent on the number of comorbidities and whether patients had a previous malignancy. As depicted in Table 3 and in the Figure, an evidence base was present for patients who had 0-1 comorbid disease and no previous malignancy (659/1,343 or 49% of all patients aged 65-75 years); partial for those who had two or more comorbid disease and no previous malignancy (498/1,343 or 37% of all patients aged 65-75 years); and limited for all patients who had a previous malignancy (186/1,343 or 14% of all patients aged 65-75 years). Contrary, the evidence base was limited for all patients aged 75 years or older, irrespective of the number of comorbidities and whether they had a previous malignancy; they were excluded from more than 60% of the randomized clinical trials solely due to age.

### Table 3. Exclusion of elderly patients with early stage breast cancer from 66 randomized clinical trials comprising the evidence base for locoregional treatment.

<table>
<thead>
<tr>
<th>Age group</th>
<th>No previous malignancy</th>
<th>Previous malignancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>65-75 years (n=1,343)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1 comorbidity</td>
<td>Number of patients (n=2,662)</td>
<td>Number of trials from which patients are excluded (n=66)</td>
</tr>
<tr>
<td>659</td>
<td>18</td>
<td>27.3</td>
</tr>
<tr>
<td>414</td>
<td>25</td>
<td>37.9</td>
</tr>
<tr>
<td>84</td>
<td>32</td>
<td>48.5</td>
</tr>
<tr>
<td>Previous malignancy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1 comorbidity</td>
<td>102</td>
<td>43</td>
</tr>
<tr>
<td>2-4 comorbidities</td>
<td>72</td>
<td>45</td>
</tr>
<tr>
<td>≥5 comorbidities</td>
<td>12</td>
<td>45</td>
</tr>
<tr>
<td>≥75 years (n=1,319)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No previous malignancy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1 comorbidity</td>
<td>459</td>
<td>40</td>
</tr>
<tr>
<td>2-4 comorbidities</td>
<td>517</td>
<td>42</td>
</tr>
<tr>
<td>≥5 comorbidities</td>
<td>138</td>
<td>44</td>
</tr>
<tr>
<td>Previous malignancy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1 comorbidity</td>
<td>84</td>
<td>52</td>
</tr>
<tr>
<td>2-4 comorbidities</td>
<td>95</td>
<td>52</td>
</tr>
<tr>
<td>≥5 comorbidities</td>
<td>26</td>
<td>52</td>
</tr>
</tbody>
</table>

* The evidence base was categorized as present (exclusion from less than 30% of the trials comprising the evidence base); partial (exclusion from 30-60% of the trials comprising the evidence base); or limited (exclusion from more than 60% of the trials comprising the evidence base).
Overall, the evidence base for locoregional treatment was present for 35%, partial for 19%, and limited for 56% of breast cancer patients aged 65 years or older with early stage disease. The evidence base for locoregional treatment in patients aged 65-75 years was dependent on the number of comorbidities, and whether patients had a previous malignancy. Contrary, the evidence base was limited in all patients aged 75 years or older. Hence, guideline recommendations regarding locoregional treatment may not necessarily be valid for patients aged ≥75 years with early stage breast cancer.

Under- or overestimation of results
The current study showed that breast cancer patients aged 75 years or older are excluded from more than 60% of the trials, and hence the evidence base was deemed limited. The evidence base in this group may be underestimated; theoretically, a large and representative sample of elderly breast cancer patients may have been included in the remaining 40% of the trials they were eligible for. On the other end of the spectrum, patients aged 65-75 years with 0-1 comorbidity and no previous malignancy were excluded from only 27% of the clinical trials and therefore, an evidence base was deemed present. However, the evidence base in the latter

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**Figure 1.** Qualification of the evidence base for locoregional treatment, for different groups of elderly breast cancer patients.

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**Discussion**

**Summary**
Overall, the evidence base for locoregional treatment was present for 35%, partial for 19%, and limited for 56% of breast cancer patients aged 65 years or older with early stage disease. The evidence base for locoregional treatment in patients aged 65-75 years was dependent on the number of comorbidities, and whether patients had a previous malignancy. Contrary, the evidence base was limited in all patients aged 75 years or older. Hence, guideline recommendations regarding locoregional treatment may not necessarily be valid for patients aged ≥75 years with early stage breast cancer.

**Under- or overestimation of results**
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group of patients may be overestimated, since it is unknown how many and which type of elderly patients are actually included in the 73% of the trials they were eligible for. Unfortunately we did not have information on the number and type of elderly patients who were actually included, since individual trial data were not available.

The results of the current study are likely to be underestimated in another manner. Disqualification of patients was assessed by eligibility criteria. However, disqualification is multifactorial; therefore, actual exclusion of elderly patients is expected to be higher, and inclusion of elderly may be even more restricted and selected. Next to eligibility criteria, physician factors, patient factors, and factors related to trial logistics may affect inclusion. These factors all favor inclusion of relatively healthy volunteers. From a patient view, age has been shown to be no significant predictor as to whether a patient would participate, once they have been offered a trial. Moreover, as exclusion criteria on comorbid disease were defined loosely, we had to specify the definition to calculate exclusion of elderly patients. As we have chosen to use a rather conservative definition, exclusion from trials due to comorbid disease is likely to be underestimated. In addition, other exclusion criteria may further affect exclusion of elderly patients. For example, 6% of the patients in the FOCUS cohort did not receive breast surgery and therefore would have been disqualified for all clinical trials in this study.

Clinical implications

Others have published on the limited inclusion of elderly patients in clinical trials. A recent literature review showed that of all clinical trials published in 2008 in five major medical journals, 20% excluded patients based on age. In the remaining trials, almost half of the trials excluded patients with age-related diseases, which could disproportionally impact inclusion of elderly patients. The novelty of the current study is that we were able to actually assess exclusion from randomized clinical trials in a large population-based cohort of elderly breast cancer patients. Hence we were able not only to evaluate the magnitude of non-evidence based medicine in elderly breast cancer patients, but also to qualify for which patients in particular an evidence base for locoregional treatment is lacking.

Recently, Wolters and colleagues compared national breast cancer guidelines from the United States of America, Canada, Australia, the United Kingdom and Germany. The authors concluded that most treatment recommendations exhibited a large degree of congruency. This was explained by the fact that they are based on the same evidence. Although the current study was based on the Dutch guideline recommendations, the study by Wolters suggests that our results may be valid to a large extent for locoregional treatment guidelines in other countries.

Breast cancer patients aged 75 years or older were excluded from the majority of the randomized clinical trials on locoregional treatment and thus, one should be aware that the evidence base for locoregional treatment in this population is limited. Extrapolation of trial results
obtained in a younger, selected population may not be justified and consequently, guidelines for locoregional treatment in early stage breast cancer may not be as valid in patients aged 75 years or older. The current findings are underlined by a previous finding that guideline adherence in elderly patients was not associated with survival\textsuperscript{29}. To enlarge the evidence base, and thereby to optimize treatment, efforts should be made to perform age specific studies in elderly patients aged 75 years or older. Moreover, relaxation of eligibility criteria that could hamper inclusion of these patients in particular\textsuperscript{30} and physician education\textsuperscript{6} and awareness may increase the number of elderly study participants.
Supplementary table 1. The evidence base for locoregional treatment, as included in the national guidelines.

Breast conserving surgery followed by radiotherapy is equally effective compared with mastectomy in terms of survival. Omission of radiotherapy after breast conserving surgery has a negative impact on locoregional control and survival. [1-11]. Meta-analyses [6]: [3,4,12-37]; [7]: [1,3-5,12-50]; [8]: [15,33-36,39-41,51].

A radiotherapy boost improves local control in all patients. The absolute benefit of a boost after complete resection declines with increasing age. [52,53]

An age of 40 years or younger is an independent predictor for a local recurrence after breast conserving surgery. [52-55]. Meta-analysis [54]: [56,57]

Good cosmesis after breast conserving surgery may be obtained in at least 70% of patients. [58]

Partial breast irradiation seems to be effective in a select group of patients with a low a priori risk for a local recurrence. [59]

Patients with large tumors (>5cm) and/or extensive nodal involvement (≥ 4 nodes involved) are at a higher risk for a locoregional recurrence, irrespective of irradical surgery and systemic therapy. [29,60,61]

In case of a mastectomy, postoperative locoregional radiotherapy decreases the risk of a locoregional recurrence with 2/3 and increases survival. [6,29,60-62]. Meta-analyses: [6]; [3,4,12-37]; [62]; [23,25-31,61,63,64]

In case of a mastectomy, locoregional radiotherapy improves local control and overall survival at 15 years of follow up, if 5 years risk of locoregional recurrence is ≥15%. [7] Meta-analysis: [7]: [1,3-5,12-50]

In case of a mastectomy, in patients with 1 to 3 positive lymph nodes, postoperative locoregional radiotherapy improves locoregional control and overall survival. [29,60,61]

Hypofractionated radiotherapy of a patient with pT1-3aN0-1M0 breast cancer with a radical resection results in comparable five years survival, local control and cosmesis compared to conventional radiotherapy schemes. [65-69]; Meta-analysis: [65]: [70,71]

Surgery of the axillary and periclavicular lymph nodes yields similar survival, disease free survival and locoregional control compared with radiotherapy, in patients with clinically node negative, operable breast cancer. [3,48]

Surgery of the axillary lymph nodes seems to yield similar survival, disease free survival and locoregional control compared with radiotherapy, in patients with clinically node positive, operable breast cancer. [3]

Risk of lymph edema and other late morbidity is higher after axillary clearance compared with radiotherapy. [72]

For references see Supplementary table 2.
Supplementary table 2. The evidence base for locoregional treatment, references.


Evidence base for locoregional treatment


Evidence base for locoregional treatment

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