Cost-effectiveness of adjuvant systemic therapy in low-risk breast cancer patients with nodal isolated tumor cells or micrometastases


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Background: The cost-effectiveness of adjuvant systemic therapy in patients with low-risk breast cancer and nodal isolated tumor cells or micrometastases is unknown.

Patients and methods: A cost-effectiveness analysis of adjuvant systemic therapy was carried out using the costs per 1% event prevented after 5 years of follow-up as incremental cost-effectiveness ratio (ICER). Secondary objective was to establish when adjuvant systemic therapy becomes cost saving. Patients included in the MIRROR study with isolated tumor cells or micrometastases who had a complete 5-year follow-up and who either did or did not receive systemic therapy were eligible. Sensitivity analyses were carried out.

Results: In the no adjuvant therapy cohort (N = 366), 24.9% of patients had an event within 5 years versus 16.8% of patients in the adjuvant therapy cohort (N = 483) (P < 0.01). The ICER was €363 per 1% event prevented. Beyond 18 years after diagnosis, the extrapolated mean cumulative costs per patient in the no adjuvant therapy cohort exceeded those of the adjuvant therapy cohort.

Conclusions: In this population of breast cancer patients with isolated tumor cells or micrometastases, €36 300 had to be invested to prevent one event in 5 years of follow-up. Adjuvant systemic therapy was cost saving beyond 18 years after diagnosis.

Key words: adjuvant systemic therapy, breast cancer, cost-effectiveness, isolated tumor cells, micrometastases

Introduction
Breast cancer is a major public health problem [1] and leads to considerable health care consumption [2]. The use of adjuvant systemic therapy has greatly improved disease-free and overall survival in patients with early breast cancer [3]. The efficacy of adjuvant systemic therapies is clearly related to prognosis: patients with high risk of recurrence benefit most of adjuvant systemic therapy. The cost-effectiveness of various adjuvant systemic therapy regimens has been reported in node-positive [4–7] and node-negative breast cancer patients [5].

Recently, we have reported the results of the Dutch MIRROR (Micrometastases or Isolated tumor cells: Relevant and Robust Or Rubbish?) study, in which (sentinel) nodal isolated tumor cells and micrometastases in patients with early-stage breast cancer and favorable primary tumor characteristics who did not receive adjuvant systemic therapy were associated with poorer disease-free survival as compared with node-negative patients. In patients with isolated tumor cells or micrometastases who received adjuvant systemic therapy, disease-free survival was improved [8].

The cost-effectiveness of administering adjuvant systemic therapy to patients with isolated tumor cells or micrometastases has never been assessed before. We present an economic analysis based on patient data derived from the MIRROR study to assess the cost-effectiveness of adjuvant systemic therapy in this patient population.

Patients and methods

Objectives
The primary objective was to determine the incremental cost-effectiveness ratio (ICER) of administration of adjuvant systemic therapy in breast
cancer patients with isolated tumor cells or micrometastases as final nodal status. The ICER was expressed as costs per 1% event prevented after 5-year follow-up. Secondary objective was to determine the time frame necessary for the administration of adjuvant systemic therapy to become cost saving (break-even point).

patients
Details of the patient and tumor characteristics in the MIRROR study have been reported elsewhere [8]. In short, all patients (N = 2707) in The Netherlands who had a sentinel node biopsy before 2006, with isolated tumor cells or micrometastases as final nodal status after central pathology revision and favorable characteristics of the primary tumor, were included, as well as a control group of node-negative patients. For the present analysis, only patients with isolated tumor cells or micrometastases who had a complete follow-up, defined as minimal follow-up of 5 years, or deceased within 5 years were eligible.

effects
An event was defined as either local, regional, or distant recurrence, contralateral invasive breast cancer, or ductal carcinoma in situ, another malignancy, death from any cause. The event rate per cohort was defined as the percentage events after 5 years of follow-up for the primary objective and as time to event for the secondary objective.

costs
volumes. Volume data on types of surgery (breast surgery, sentinel node biopsy, and optionally axillary lymph node dissection), application of radiotherapy, administration (type and duration) of adjuvant systemic therapy, and on frequency and type of recurrence of disease were derived from patients in the no adjuvant and adjuvant therapy cohort. In addition, we used data from other sources to assess the frequency of adverse events of sentinel node biopsy, axillary lymph node dissection [9–11], and adjuvant systemic therapy [12–14]. The Dutch guidelines for treatment of breast cancer were used to determine the cost parameters for uncomplicated follow-up and the treatment of local, regional, and contralateral recurrences [15]. The mean costs of diagnosis and treatment of metastatic breast cancer from 2004 to 2009 were derived from a random selection of 50 patients not included in this study treated in a university hospital that also provides a regional function. All cost data, except the costs of diagnosis and treatment of metastatic breast cancer, were based on samples of patients with complete follow-up in the no adjuvant and adjuvant therapy cohort. The mean costs of diagnosis and treatment of metastatic breast cancer were added to these costs as a constant to those patients who developed metastatic breast cancer in the respective cohorts.

cost prices. Supplemental Table S1 (available at Annals of Oncology online) shows the unit cost price and their sources. In accordance with national guidelines for cost calculation in health care, we added 35% overhead costs to cost of personnel [17]. We calculated full cost prices from date of diagnosis up to 5 years after diagnosis for every treatment delivered for primary breast cancer, follow-up, and local, regional, contralateral, or distant recurrence of disease. All costs were converted to 2008 Euros using the Dutch consumer price index [20].

cost and effect analyses
Costs were discounted to present values at 3%. Cost differences between both cohorts were explored by linear regression. First, a linear regression model was fitted to the raw data without taking into account potential confounding. Second, a regression model taking into account potential confounders (age, nodal status, log tumor size, tumor grade, and axillary treatment) was fitted to the data. Event rates after 5 years of follow-up were analyzed in a similar way with a generalized linear model (binomial family) using an identity link.

To assess the secondary objective, we analyzed the expected disease-free survival with a parametric regression model using the set of confounders described above and assuming a log-logistic distribution for the disease-free survival times. The costs up to break-even were assessed using the mean costs of follow-up with adding the expected event rates per cohort, derived from the parametric regression model multiplied by the mean costs of an event.

cost-effectiveness analysis
We carried out a cost-effectiveness analysis from an inpatient perspective. The sample for this analysis was bootstrapped (N = 1000) to derive a fairly normal distribution of the ICER. The 95% confidence interval (95% CI) of the ICER(s) was estimated using the percentile method. Finally, cost-effectiveness acceptability curves (CEACs) were derived enabling to evaluate efficiency by exploring a range of thresholds (willingness to pay for 1% event prevented in 5 years) [21]. The CEAC shows how many of all bootstrap replications, expressed as the probability (y-axis), result in ICERs lower than or equal to a certain willingness to pay for 1% event prevented (x-axis). For an increasing willingness to pay for 1% event prevented in 5 years, the probability that adjuvant systemic therapy becomes cost-effective increases according to the shape of the acceptability curve.

sensitivity analyses
One-way sensitivity analyses were carried out on the status of the follow-up: a pessimistic scenario on complete and incomplete follow-up, an optimistic scenario on complete follow-up or incomplete follow-up and the occurrence of an event within 5 years, and two scenarios in which the discount rates were varied between 0% and 6%. These sensitivity analyses were displayed as CEACs. One additional deterministic scenario was carried out in which patients receiving chemotherapy in the base-case analysis received a third-generation chemotherapy regimen [six cycles of docetaxel, doxorubicin and cyclophosphamide (TAC)] instead of a first or second-generation regimen, taking into account additional costs and effectiveness [22].

results
patients
Complete follow-up up to 5 years after diagnosis was available for 366 of 856 patients (43%) in the no adjuvant therapy cohort and for 483 of 995 patients (49%) in the adjuvant therapy cohort of the MIRROR study. The characteristics of the patients with complete follow-up in the no adjuvant therapy cohort (N = 366) and the adjuvant therapy cohort (N = 483) are shown in Table 1.

effects
Of patients with a complete follow-up, 24.9% had an event within 5 years in the no adjuvant therapy cohort and 16.8% of patients in the adjuvant therapy cohort. The difference in event rates between the cohorts was 8.1% (95% CI 2.6% to 13.6%). After correction for confounders, the difference in events between the cohorts was 8.0% (95% CI 2.4% to 13.6%).
costs
From a random selection of 50 patients with metastatic breast cancer, 46 patients had a follow-up of at least 1 year, and 27 patients had a follow-up of at least 2 years and could be included in the analysis of costs. The mean costs of diagnosis and treatment of metastatic breast cancer for the first year after diagnosis of metastatic disease were €19 156 (N = 46; 95% CI €11 589–€26 722). The mean costs of treatment for the second year after diagnosis of metastatic disease were €15 622 (N = 27; 95% CI €9 260–€21 985). These costs were assigned to the patients with metastatic disease in the present study.

Figure 1 shows the mean categorized cumulative costs per patient in the no adjuvant and the adjuvant therapy cohort. After the first year of diagnosis, the additional costs per patient comprised adjuvant systemic therapy (endocrine treatment) in the adjuvant therapy cohort and costs due to recurrence of disease and follow-up in both cohorts. The estimated mean total costs after 5 years of follow-up were €15 119 (95% CI €14 034–€16 205) for the patients in the no adjuvant therapy cohort and €18 059 (95% CI €17 277–€18 840) for the patients in the adjuvant therapy cohort, resulting in a difference of €2939 (95% CI €16 383–€4241). After correction for confounders, the difference in mean total costs remained significant, however, smaller [€18 52 (95% CI €4 59–€32 45)].

The difference in total mean costs per patient between both cohorts could be attributed to higher costs for primary surgical, radiotherapeutic, and adjuvant systemic treatment and lower costs for recurrence of disease in the adjuvant therapy cohort.

cost-effectiveness
The base-case scenario showed an ICER of €363 per 1% event prevented in 5 years (95% CI −€1 422 to €4 159). The base-case CEAC is displayed in Figure 2. The willingness to pay for 1% event prevented in 5 years, given an 80% probability that adjuvant systemic therapy becomes cost-effective, approached €1000.

the break-even point for adjuvant systemic therapy
The mean costs for recurrence of disease were €16 809 in the no adjuvant therapy cohort and €11 627 in the adjuvant therapy cohort. The mean costs of follow-up in the fifth year after diagnosis of metastatic disease were €19 156 (N = 46; 95% CI €11 589–€26 722). The mean costs of treatment for the second year after diagnosis of metastatic disease were €15 622 (N = 27; 95% CI €9 260–€21 985). These costs were assigned to the patients with metastatic disease in the present study.

Table 1. Characteristics of patients in the no adjuvant therapy cohort and the adjuvant therapy cohort

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No adjuvant therapy cohort</th>
<th>P value</th>
<th>Adjuvant therapy cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>(N = 366), N (%)</td>
<td>(N = 483), N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Years of age (median (range))</td>
<td>57 (32–89)</td>
<td>0.58</td>
<td>57 (31–88)</td>
</tr>
<tr>
<td>Tumor size</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤1 cm</td>
<td>100 (27)</td>
<td>0.02</td>
<td>99 (23)</td>
</tr>
<tr>
<td>1–2 cm</td>
<td>214 (59)</td>
<td>290 (59)</td>
<td></td>
</tr>
<tr>
<td>2–3 cm</td>
<td>52 (14)</td>
<td>94 (17)</td>
<td></td>
</tr>
<tr>
<td>Tumor grade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>133 (37)</td>
<td>0.02</td>
<td>134 (28)</td>
</tr>
<tr>
<td>2</td>
<td>213 (60)</td>
<td>325 (68)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>12 (3)</td>
<td>17 (4)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>8 (0)</td>
<td>7 (0)</td>
<td></td>
</tr>
<tr>
<td>ER/PgR status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER+ and/or PgR+</td>
<td>322 (91)</td>
<td>0.02</td>
<td>450 (95)</td>
</tr>
<tr>
<td>ER− and PgR−</td>
<td>31 (9)</td>
<td>23 (5)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>13 (0)</td>
<td>10 (0)</td>
<td></td>
</tr>
<tr>
<td>Final nodal status (revised)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pN0(i+)</td>
<td>259 (71)</td>
<td>&lt; 0.01</td>
<td>183 (38)</td>
</tr>
<tr>
<td>pN1mi</td>
<td>107 (29)</td>
<td>300 (62)</td>
<td></td>
</tr>
<tr>
<td>ALND and/or AI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No ALND and/or AI</td>
<td>193 (53)</td>
<td>&lt; 0.01</td>
<td>80 (17)</td>
</tr>
<tr>
<td>ALND and/or AI</td>
<td>173 (47)</td>
<td>403 (83)</td>
<td></td>
</tr>
<tr>
<td>Systemic adjuvant therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hormonal therapy</td>
<td>—</td>
<td>NA</td>
<td>316 (65)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>—</td>
<td>40 (8)</td>
<td></td>
</tr>
<tr>
<td>Both</td>
<td>—</td>
<td>127 (26)</td>
<td></td>
</tr>
</tbody>
</table>

AI, axillary irradiation; ALND, axillary lymph node dissection; ER, estrogen receptor; NA, non applicable; PgR, progesterone receptor.

Figure 1. Mean cumulative costs per patient in the no adjuvant and the adjuvant therapy cohort, classified by type of costs.
after diagnosis were €128. Figure 3 shows the extrapolated cumulative mean costs per patient up to 20 years after diagnosis in both cohorts, using the extrapolated event rate. Around 18 years after diagnosis, the extrapolated mean cumulative costs per patient were almost equal in the no adjuvant therapy cohort (€22,652) as compared with the adjuvant therapy cohort (€22,694) and consequently, the no adjuvant systemic therapy and the adjuvant systemic therapy strategy approach breakeven. Beyond 18 years after diagnosis, adjuvant systemic therapy becomes the dominant strategy, i.e. cost saving and more effective.

sensitivity analyses
Sensitivity analyses resulted in ICERs ranging from €129 to €478 for 1% event prevented. Figure 2 shows the CEACs for the different scenarios. Varying the discount rate did not alter the results in any way. The optimistic scenario showed that the willingness to pay for 1% event prevented in 5 years with a 95% probability that adjuvant systemic therapy became cost-effective approached €500; the pessimistic scenario resulted in a willingness to pay for 1% event prevented in 5 years with a 80% probability that adjuvant systemic therapy became cost-effective approached €1200. The deterministic established scenario, the administration of six cycles of TAC, resulted in an ICER of €743 per 1% event prevented.

discussion
The MIRROR study has shown that disease-free survival was decreased in patients with isolated tumor cells or micrometastases as compared with node-negative patients and significantly improved in patients with isolated tumor cells or micrometastases who received adjuvant systemic therapy [8]. The present study assessed whether the administration of adjuvant systemic therapy in patients with early-stage breast

### Table 2. Difference in mean costs per patient between the adjuvant therapy cohort and the no adjuvant therapy cohort after 5 years of follow-up

<table>
<thead>
<tr>
<th></th>
<th>Differences in mean costs per patient (adjuvant therapy cohort minus no adjuvant therapy cohort)</th>
<th>95% CI of difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total costs</td>
<td>€2939</td>
<td>€1603–€4275</td>
</tr>
<tr>
<td>Primary treatment</td>
<td>€1725</td>
<td>€1180–€2268</td>
</tr>
<tr>
<td>AST</td>
<td>€3008</td>
<td>€2669–€3348</td>
</tr>
<tr>
<td>Follow-up</td>
<td>–€9</td>
<td>–€31–€14</td>
</tr>
<tr>
<td>Recurrence of disease</td>
<td>–€1785</td>
<td>–€2982 to –€589</td>
</tr>
</tbody>
</table>

*Primary treatment = surgery and optionally irradiation.

AST, adjuvant systemic therapy; CI, confidence interval.

Figure 2. Cost-effectiveness acceptability curves for the base case scenario and the scenarios in the sensitivity analyses.
generation chemotherapy regimen (TAC) was applied, resulted...

...practice. The deterministic scenario, in which a third-
...micrometastases is cost-effective. Cancer and lymph
...cells or micrometastases was expected to become
...saving far before a substantial part of the patients
...saving of costs. The mean age of patients in this
...expected to become dominant, resulting in both
...disease recurrence in this study are expected to die.

This study is a nationwide cohort study in an unselected
...treatment in the adjuvant therapy cohort, the mean costs
...hazardly small but remained significant. In the
...effect on the cost-effectiveness. In our cohort study,
...the follow-up duration was 5 years. In the cost-effectiveness
...follow-up of at least 5 years. In the scenario where patients
...frequently occurs >10 years after diagnosis [23]. To assess
...and consequently would become cost saving, we extrapolated
...years after diagnosis, the expected mean costs in both
...adjuvant systemic therapy becomes cost saving far before
...part of the patients without disease recurrence in this study
...expected to die. This study is a nationwide cohort study
...patient population, reflecting daily clinical practice. Due to
...and the more frequent axillary treatment in the adjuvant
...cohort, the mean costs per patient were higher as compared
...correction for confounders, the difference between both
...smaller and remained significant. In the sensitivity analyses,
...cost of costs had negligible effect on the cost-effectiveness.
...in our cohort study, the average follow-up duration was
...in the study population, €36 300 has to be invested extra.
...breast cancer, disease recurrence frequently occurs >10 years
...disease recurrence in this study is expected to die.

Annals of Oncology/online) and only 1.25 times more effectiveness
...cost-utility of first-generation chemotherapy regimens in
...cost-effectiveness and cost-utility analyses have been carried
...patients [30] studied first-generation chemotherapy regimens in
...was analyzed in node-positive patients [6, 7, 31–33], resulting
...363 per 1% event prevented after 5 years of follow-up. An alternative
...this regimen also showed to be more effective than second-
...patients [27]. Probably, in the near future, all breast cancer
...adjuvant chemotherapy will receive a third-generation regimen,
...adjuvant systemic therapy in node positive and in both node
...trastuzumab is currently used as adjuvant targeted therapy in
...HER2-positive breast cancer who are candidates for adjuvant
...adjuvant systemic therapy in the current era. In addition,
...hormonal therapy instead of hormonal therapy only. As the
guidelines for adjuvant systemic therapy have become more
...liberal nowadays [15, 25], this scenario better reflects
...practice. The deterministic scenario, in which a third-
...generation chemotherapy regimen (TAC) was applied, resulted
...in the most unfavorable cost-effectiveness of all scenarios. This
...was mainly due to more than six times higher costs of adjuvant
...systemic therapy Supplemental Table S1 (available at Annals of
...Oncology online) and only 1.25 times more effectiveness [22]
in the adjuvant therapy cohort. Like in node-positive patients
...recently, this regimen also showed to be more effective than second-
generation regimens in node-negative patients [27]. Probably, in
the near future, all breast cancer patients who need adjuvant
chemotherapy will receive a third-generation regimen, and therefore,
this scenario might reflect future practice. In this study, 59% of patients
on endocrine therapy received tamoxifen for 5 years. Currently, this
therapy will mostly consist of 2–3 years of tamoxifen, followed by
2–3 years of a more expensive Supplemental Table S1 (available at
Annals of Oncology online) but more effective [28] aromatase
inhibitor. This will change the cost-effectiveness of adjuvant
systemic therapy in the current era. In addition, trastuzumab is
currently used as adjuvant targeted therapy in patients with
HER2-positive breast cancer who are candidates for adjuvant
chemotherapy [29]. This effective but expensive drug will
change the cost-effectiveness of adjuvant systemic therapy in
HER2-positive breast cancer patients even more.

In various breast cancer patient populations, cost-
effectiveness and cost–utility studies have been carried out.
Messori et al. [4] and Kievit et al. [30] studied first-generation
chemotherapy regimens in node positive and in both node
negative and positive patients, respectively, resulting in ICERs
of $23 000 and €4837 per life year gained, the last study
including also endocrine therapy. Recently, the cost-utility of
third versus second-generation chemotherapy regimens were
analyzed in node-positive patients [6, 7, 31–33], resulting in
ICERs of $2631/QALY (quality-adjusted life year) [31] up to
GBP20432/QALY [6]. Adjuvant systemic therapy is less
cost-effective in patients with lower risk of disease recurrence,
illustrated by Kattlove et al. [5], who showed that an
investment of $50 000 was necessary to save one life in 10
years in node-negative patients who received
cyclophosphamide, methotrexate, 5-fluorouracil (CMF)
polychemotherapy versus no chemotherapy, versus an
investment of $23 000 in node-positive breast cancer patients.
These economic analyses are difficult to compare, as the
included patients’ risk profiles and the timeframes for costs
...cancers.
and effects vary, different end points have been used, and sensitivity analyses and discounting have not always been carried out. In patients with nodal isolated tumor cells or micrometastases, cost-effectiveness or cost-utility analyses have never been reported.

In The Netherlands, treatment of serious diseases is considered cost-effective if costs of treatment do not exceed €80 000 per QALY [34]. In our study, we did not have data with respect to quality of life (QoL) of the included patients. However, QALY is not a very common parameter in economic analyses of adjuvant systemic therapy in breast cancer, as the impact of adjuvant systemic therapy on QoL is transient and minor compared with patients’ adaptation and coping after diagnosis and surgery [35]. Moreover, recurrence of disease is associated with decrease in QoL, which we have taken into account by using the percentage of events prevented as effect parameter. Finally, QoL is less important as administering adjuvant systemic therapy was not only expected to be more effective but also cost saving beyond 18 years of follow-up.

This study was carried out in The Netherlands. As health care policies and costs of treatment might vary, the exact results of this cost-effectiveness analysis may be difficult to extrapolate to other countries. However, as adjuvant systemic therapy was expected to become cost saving beyond 18 years of follow-up, it seems reasonable to assume that in the long run adjuvant therapy becomes cost saving in all Western countries. This study was carried out from an inpatient perspective. Therefore, costs for extramural care were not taken into account. Especially in metastatic disease, these costs can be considerable, accounting for almost 15% of total costs of metastatic disease [36]. If extramural costs would have been taken into account, the administration of adjuvant systemic therapy was expected to become more cost-effective, as more patients in the no adjuvant therapy cohort had distant metastatic disease.

In conclusion, we carried out a cost-effectiveness analysis within a large nationwide cohort study to assess the cost-effectiveness of administering adjuvant systemic therapy to patients with nodal isolated tumor cells or micrometastases. To prevent one event in 5 years in this population of early breast cancer patients, €36 300 had to be invested to be considered cost-effective. Beyond 18 years after diagnosis, the administration of adjuvant systemic therapy in this population was cost saving.

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references


disclosure

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Long-term cosmetic changes after breast-conserving treatment of patients with stage I–II breast cancer and included in the EORTC ‘boost versus no boost’ trial

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Background: In breast cancer treated with breast-conserving radiotherapy, the influence of the boost dose on cosmetic outcome after long-term follow-up is unknown.

Patients and methods: We included 348 patients participating in the EORTC ‘boost versus no boost’ mega trial with a minimum follow-up of 6 years. Digitalised pictures were analysed using specific software, enabling quantification of seven relative asymmetry features associated with different aspects of fibrosis.

Results: After 3 years, we noted a statistically significantly poorer outcome for the boost patients for six features compared with those of the no boost patients. Up to 9 years of follow-up, results continued to worsen in the same...