Long-term follow-up of the SBG 9401 study comparing tailored FEC-based therapy versus marrow-supported high-dose therapy


On behalf of the Scandinavian Breast Group, study SBG 9401

Background: The purpose was to investigate adjuvant marrow-supportive high-dose chemotherapy compared with an equitoxicity-tailored comparator arm.

Patients and methods: Five hundred and twenty-five women below the age of 60 years with operated high-risk primary breast cancer were randomised to nine cycles of granulocyte colony-stimulating factor supported and individually tailored FEC (5-fluorouracil, epirubicin, cyclophosphamide), (n = 251) or standard FEC followed by marrow-supported high-dose therapy with CTCb (cyclophosphamide, thiotepa, carboplatin) therapy (n = 274), followed by locoregional radiotherapy and tamoxifen for 5 years.

Results: There were 104 breast cancer relapses in the tailored FEC group versus 139 in the CTCb group (double triangular method by Whitehead, P = 0.046), with a median follow-up of all included patients of 60.8 months. The event-free survival demonstrated 121 and 150 events in the tailored FEC- and CTCb group, respectively [P = 0.074, hazard ratio (HR) 0.804, 95% confidence interval (CI) 0.633–1.022]. Ten patients in the tailored FEC regimen developed acute myeloid leukaemia (AML)/myelodysplasia (MDS). One hundred deaths occurred in the tailored FEC group and 121 in the CTCb group ([P = 0.287, HR 0.866, 95% CI 0.665–1.129].

Conclusion: The update of this study shows an improved outcome linked to the tailored FEC treatment in relation to breast cancer relapse, but also an increased incidence of AML/MDS.

Key words: adjuvant, breast cancer, randomised, tailored chemotherapy

Introduction

Surgery is the primary treatment of early breast cancer, but medical treatment as well as radiotherapy have become corner stones in the management of primary breast cancer as adjuvant treatment. These therapies, alone or in combination, have been shown to result in survival gains, when added to surgery [1, 2]. With respect to chemotherapy, a dose–response relationship has been demonstrated for some of the drugs and combinations used during the last decades [3].

In the adjuvant setting, conventionally escalated higher doses of epirubicin have resulted in improved outcome [4]. On the other hand, conventionally escalated or higher than normal doses of doxorubicin or cyclophosphamide did not result in improved outcome [5–7]. To further evaluate the dose–response concept, even higher chemotherapy doses requiring autologous bone marrow support have been tested in multiple phase I and II studies. Due to the initially very promising results from these studies compared with historical outcome data, 12 randomised studies were initiated and have been reported as full papers exploring the use of adjuvant marrow-supported, high-dose therapy [8–19].

We have previously reported the SBG 94-01 trial, comparing tailored FEC (5-fluorouracil (5-FU), epirubicin (Epi),...
cyclophosphamide (C) with bone marrow-supported therapy, at a median follow-up of 34.3 months [8]. In that report, we found 81 breast cancer relapses in the tailored FEC group compared with 113 in the CTCb (cyclophosphamide, thiopeta, carboplatin) group (double triangular method \( P = 0.04 \)). At that time, we also reported nine patients with acute myeloid leukaemia (AML)/ myelodysplasia (MDS) in the tailored FEC arm and found no overall survival (OS) benefit (log-rank \( P = 0.12 \)).

In this publication, we report on the update of the study with a median follow-up of five years.

patients and methods

study design

The SBG 9401 study was a prospective and randomised trial comparing three courses of standard FEC followed by autologous marrow-supported high-dose therapy compared with nine courses of tailored and dose-escalated FEC as a comparator arm. The rationale behind the trial as well as the trial design has previously been described in detail [8].

The primary end point was time to breast cancer relapse or breast cancer death, termed disease-free survival in the study protocol. Secondary end points were OS, safety, dose intensity, total chemotherapy doses, data on peripheral blood stem cells harvest and time to marrow reconstitution. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria.

In this update, we also report on a retrospectively defined end point: event-free survival (EFS). EFS is defined as any of the following events: breast cancer relapse, breast cancer death, contralateral breast cancer, other malignancies including AML/MDS and death without breast cancer.

eligibility

Breast cancer patients younger than 60 years of age with eight or more positive axillary lymph nodes or five or more positive axillary lymph nodes in combination with negative hormone receptors and either high S-phase or nuclear anaplasia grade 2–3 (or an equivalent high-grade criterion) were eligible for the study. Patients were required to have a normal chest X-ray as well as adequate cardiac, liver and renal function. Patients had to be operated either with mastectomy or with breast-conserving surgery. Patients with proven distant metastases or a previous cancer were ineligible; however patients with light microscopic signs of cancer cells in the bilateral iliac biopsies were allowed to participate in order to avoid stage migration. Accordingly, patients with local hot uptakes on bone scan, but with a normal conventional X-ray of the skeleton were also included, this strategy was aimed at avoiding stage migration.

The study was approved by the ethical committees with jurisdiction for the participating centres.

All patients had given written informed consent.

randomisation procedure

Eligible patients who gave consent were randomised by telephone by the national study trial centres. Patients were stratified on the basis of the presence or absence of light microscopic bone marrow metastases at the time of randomisation.

Table 1. Given doses and dose adjustments

<table>
<thead>
<tr>
<th>Step</th>
<th>5-FU mg/m²</th>
<th>Epirubicin mg/m²</th>
<th>Cyclophosphamide mg/m²</th>
<th>Mesna mg/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>600</td>
<td>60</td>
<td>900</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>600</td>
<td>90</td>
<td>1200</td>
<td>240</td>
</tr>
<tr>
<td>3</td>
<td>600</td>
<td>105</td>
<td>1500</td>
<td>300</td>
</tr>
<tr>
<td>4</td>
<td>600</td>
<td>120</td>
<td>1800</td>
<td>360</td>
</tr>
</tbody>
</table>

Cycle length, 3 weeks; treatment period, nine courses.

Course 1 should be given according to step 1.

Course 2–9 according to Table 2.

blood cell (WBC) count, platelets and haemoglobin were analysed. On the basis of the WBC and platelet cell counts, the doses were adjusted aiming at an equivalent WBC and platelet toxicity for each of the following courses (Table 2).

Patients who were randomly assigned to the autologous marrow-supportive high-dose chemotherapy arm were treated with three courses of \( F_{600E60C600} \) (mg/m²), if for administrative reasons the marrow-supported supportive high-dose chemotherapy arm were treated with three courses of \( F_{600E60C600} \); for the third course, a fourth course of standard \( F_{600E60C600} \) was recommended. To facilitate harvest of peripheral blood stem cells, the cyclophosphamide dose at the third FEC course was escalated to 1200 mg/m² together with filgrastim at 5 \( \mu \)g/kg. CTCb (6000 mg/m² cyclophosphamide, 500 mg/m² thiotepa and 800 mg/m² carboplatin) was given as intravenous infusion over 4 days on days 7 to 10 and the stored autologous peripheral stem cells with a recommended dose of at least \( 2 \times 10^{10} \) CD34+ cells/kg were transfused on day 0. These patients were started on filgrastim at 5 \( \mu \)g/kg, the day after marrow transfusion.

All randomised patients received locoregional radiotherapy in 2 Gy fractions, 5 fractions/week, to a total dose of 46–50 Gy. The target volumes were mastectomy scar area or breast parenchyma, axillary-, supraclavicular-/ infraclavicular- and parasternal lymph nodes. The latter lymph nodes were only included if considered to be technical feasible or not resulting in too high doses into the myocardium.

All patients were given tamoxifen at 20 mg per day for 5 years nonconcurrently with the delivered chemotherapy and irrespective of hormone receptor status.

statistical methods

All analyses were carried out on the basis of the intention-to-treat. For the primary aim, the double triangular sequential trial method according to Whitehead was used initially aiming at detecting a difference of 55% in median recurrence-free survival (from 52–81 months) with the significance level of 5% and the power of 80% with an initial sample size of 320 patients, later expanded to 500 patients with a planned further inclusion, which was stopped at 525 patients due to AML/MDS in the tailored FEC arm [8]. For OS and for EFS we used a double-sided log-rank test.

results

The SBG 9401 study was open for recruitment during a 4-year period from 1994 to 1998. Five hundred and twenty-five patients were included, 251 were randomised to tailored and dose-escalated FEC and 274 were randomised to standard FEC followed by marrow-supportive high-dose therapy. The groups were well balanced as previously reported.
We have previously reported at a median follow-up of 34.3 months that there were 81 breast cancer relapses in the tailored FEC group versus 113 in the CTCb group ($P = 0.04$ using the predefined double triangular method). With respect to OS, there were 60 deaths in the tailored FEC group and 82 in the marrow-supportive high-dose group (log-rank $P = 0.12$). We also reported on statistically significant more grade 3 or 4 acute toxicity in the CTCb group compared with the tailored FEC group. Two patients died during the marrow-supportive high-dose procedure and at the previous publication we reported on nine patients who developed AML or MDS; all in the tailored FEC group.

For the present long-term follow-up with a median follow-up at 60.8 months (data lock for follow-up time was 26 May 2003), there were 104 breast cancer relapses in the tailored FEC group compared with 139 relapses in the standard FEC group followed by marrow-supportive high-dose therapy ($P = 0.046$ according to the double triangular method) [log-rank $P = 0.019$, hazard ratio (HR) 0.739, 95% confidence interval (CI) 0.573–0.953] (Figure 1).

The pattern of relapse in relation to receptor status shows that most recurrences for the receptor-negative group occur within the first 3–4 years, while patients with receptor-positive breast cancers (oestrogen and/or progesterone receptor) have a prolonged risk of relapse (Figure 2).

The relapse patterns were similar irrespective of delivered chemotherapy dose levels in the tailored dose-escalated FEC arm (Figure 3).

For EFS, we had 121 and 150 events in the tailored FEC arm and CTCb arm, respectively. The median follow-up for all patients in this analysis was 59.7 months (Figure 4). This difference is not statistically significant (log-rank $P = 0.074$, HR 0.804, 95% CI 0.633–1.022). Reported events (patients can here be listed for several events per patient) in the analysis in relation to allocated treatment (tailored FEC/CTCb) were breast cancer relapse 104/139, contralateral breast cancer (seven/nine) (FEC: one patient had both a contralateral breast cancer and a rectal cancer; CTCb: three patients with contralateral cancer also had a breast cancer relapse) AML and/or MDS (ten/zero) (one patient in the FEC arm developed a rectal and skin cancer, in addition to MDS), other malignancies (four/six) and death without breast cancer relapse (eleven/four).

We registered 100 deaths in the tailored FEC group and 121 in the CTCb group ($P = 0.287$, HR 0.886, 95% CI 0.665–1.129). This is on the basis of a median follow-up for all patients of 65.4 months.

In the present follow-up there is one additional patient who has developed AML/MDS, bringing the total figure to 10 patients in the tailored FEC arm, resulting in a total risk of 3.98% (95% CI 0.019–0.0072).

In the first publication of the SBG 9401 study, we reported on seven patients in the FEC arm with cardiac side-effects and four in the CTCb arm. In the present follow-up there are four additional patients in the FEC arm and one more in the CTCb arm since the last follow-up.

**Discussion**

The present update of the SBG 9401 study is in line with the previous report and show fewer breast cancer relapses in the

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**Table 2. Dose reduction schedule**

<table>
<thead>
<tr>
<th>Nadir day 8, 11/12 or 15</th>
<th>Day 8, 11/12 or 15 (except nadir value)</th>
<th>Day 22</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC Platelets</td>
<td>WBC Platelets</td>
<td>WBC Platelets</td>
<td></td>
</tr>
<tr>
<td>&gt;1.0 &gt;50 and</td>
<td>21.5 275 and</td>
<td>≥3.0 and 2100</td>
<td>Dose escalation. Continue to next step.</td>
</tr>
<tr>
<td>≤1.0 ≤50 and/or</td>
<td>&lt;1.5 &lt;75 and</td>
<td>≥3.0 and 2100</td>
<td>Stay on same step for next course.</td>
</tr>
<tr>
<td>any ≤15 and/or</td>
<td>any any any and</td>
<td>any any 2100</td>
<td>Reduce one step and/or other treatment</td>
</tr>
<tr>
<td>&gt;1.0 &gt;50 and</td>
<td>21.5 275 and</td>
<td>2.5–2.9 and 2100</td>
<td>Stay on same step for next course</td>
</tr>
<tr>
<td>any any any</td>
<td>any any any and</td>
<td>2.0–2.9 and 75–99</td>
<td>Reduce one step. If this is tolerated—escalate according to schedule again</td>
</tr>
<tr>
<td>any any any</td>
<td>any any any and</td>
<td>&lt;2 and/or &lt;75</td>
<td>Delay 1 week. When normal values—reduce one step, but 2 step 1</td>
</tr>
</tbody>
</table>

WBC, white blood cells $\times 10^9/L$; Platelets $\times 10^9/L$.

**Figure 1.** Kaplan–Meier plot of breast cancer relapse or breast cancer death for the tailored 5-fluorouracil, epirubicin, cyclophosphamide (FEC) versus cyclophosphamide, thiotepa, carboplatin (CTCb) arm. Patients in the FEC arm are indicated with a solid line, while patients in the CTCb arm are outlined in the dotted line ($P = 0.046$ according to the double triangular method) [log-rank $P = 0.019$, hazard ratio (HR) 0.739, 95% confidence interval (CI) 0.573–0.953] (Figure 1).

**Figure 2.** Breast cancer relapse-free survival (FEC—A-arm vs CTCb—B-arm). Median follow-up 60.8 months (censored = 75.2 months).
compared with the marrow-supportive high-dose therapy arm. These results, at a median follow-up for all patients of 60.8 months, contain mature data as the study included very high-risk primary breast cancer patients.

The observed lack of an OS benefit by haematopoietic stem cell-supported high-dose therapy as adjuvant breast cancer therapy to patients with a high risk of relapse is in line with several other prospective and randomised studies [8, 10–12, 14–18, 20]. One recently reported study, using a dose-dense strategy with early intensification, has shown contradictory results with an OS gain for the marrow-supported high-dose arm [13], while four of the studies including the SBG 9401 study demonstrated partly opposite findings [9, 14, 21]. These studies are all characterised by at least eight courses of conventional polychemotherapy or by the use of dose-dense and taxane-containing regimen or by use of the tailored FEC regimen, all of these regimens could potentially be considered to be more optimal and better control arms.

The reason for the negative outcome of many of the individual studies may reflect breast cancer biology, which for most patients is characterised by a rather slow proliferation rate. Thus, the impact of a single course of marrow-supportive high-dose therapy by cytostatics, mostly alkylating agents, could therefore be discussed. In addition, most of the studies have been of moderate size and of low power. A way to identify subgroups with an eventual benefit from higher chemotherapy doses or dose intensification would be to carry out a meta-analysis, which also can reveal overall smaller benefits. Such efforts are ongoing.

Rodenhuis et al. [22] have, however, demonstrated an improved relapse-free survival for patients with HER2/neu-negative tumours receiving marrow-supported high-dose therapy [11]. These data indicate that marrow-supported high-dose therapy may be beneficial for some patients with HER2/neu-negative cancers.

We have recently published on the SBG 9401 study that 48 of 128 patients with HER2/neu-amplified cancers (representing 32.7%, 391 analysed samples) also had an amplification of topoisoerase II alpha gene [23]. These patients had fewer breast cancer relapses ($P = 0.049$) when receiving tailored FEC, containing much higher Epi doses compared with the CTCb arm. The effect is potentially explained by Epi binding to the anthracycline targets on the topoisoerase II alpha protein [23].
Unfortunately, we lack information on menstrual status of patients after completion of chemotherapy. One may speculate that patients in the tailored FEC group obtained a higher rate of ovarian ablation, which could contribute to fewer relapses for the subgroup of patients with receptor-positive disease \( (P = 0.034, HR 0.687 \ [95\% \ CI 0.484–0.974]) \), not seen to the same extent in the receptor negative group \( (P = 0.224, HR 0.783 \ [95\% \ CI 0.527–1.163]) \) (Figure 2).

The so far published studies represent different designs with different comparator arms compared with the marrow-supportive high-dose arms. Our comparator arm, not being a classical control arm, should be seen in the context of the search for an optimised anthracycline-based regimen not requiring the autologous marrow-supportive strategy. One should observe that patients in the tailored FEC arm actually received higher total doses of both Epi and C, compared with patients in the CTCb arm. The median total dose C was 10,238 mg/m² in the tailored FEC arm. Corresponding dose in the CTCb arm was 8,400 mg/m². The Epi dose was 780 mg/m² in the tailored and dose-escalated FEC group and 181 mg/m² in the CTCb arm. The 5-FU dose was also higher in the tailored FEC arm. These data, from a single study, indicate that higher cumulative doses were of benefit with reference to breast cancer outcome, keeping in mind that the drugs were delivered in repeated courses in a tailored fashion and not as a single course. The importance of repeated higher doses is supported by Nitz et al. [13] and Basser et al. [15].

The importance of the tailoring chemotherapy on the basis of toxicity is further supported by this updated report, demonstrating similar outcomes irrespective of delivered and tailored chemotherapy doses. The individual tolerance to chemotherapy is likely a refection of multiple, so far, not fully explored factors. Such factors could include differences in the expression of genes/enzymes involved in the metabolism of the anticancer drugs, as well as a genetically different tolerances to these drugs on the basis of the single nucleotide polymorphism patterns in normal cells and in the corresponding cancer cells in each individual patient. Six retrospective studies with 3356 patients have revealed an inferior outcome for patients receiving adjuvant chemotherapy without toxicity or full chemotherapy doses, compared with those who experienced haematological toxicity, in one study moderate (grade 2–3) granulocyte toxicity [24–29]. We have only identified one negative report with 236 breast cancer patients not confirming the data from the other studies [30].

The major downside with the tailored and dose-escalated FEC arm was the increased risk for secondary AML/MDS. Six of the patients developed AML/MDS within 2 years and eight within 3 years from start of adjuvant chemotherapy. The reason for the increased risk for secondary AML/MDS is not known. The tailored FEC regimen includes several potential risk factors for bone marrow disturbances as high cumulative doses of epirubicin and cyclophosphamide, granulocyte colony-stimulating factor (G-CSF) exposure and radiotherapy [31]. More recently, the importance of irradiated target volumes potentially in relation to higher anthracycline doses has been discussed [32]. In our study, not one of the patients in the CTCb arm developed a secondary AML/MDS despite receiving equivalent radiotherapy volumes. Accordingly, one may speculate that the very high dose of epirubicin in the tailored FEC arm compared with the CTCb arm (780 versus 181 mg/m², respectively) may be extra harmful in combination with the relatively large postoperative target volume which was used in this study. Due to the AML/MDS toxicity, we modified the original tailored FEC regimen and we are therefore using a modified tailored FEC regimen including only six courses. The maximal cyclophosphamide dose has also been reduced to 1200 mg/m² per course and G-CSF is only delivered from days 5 to 12. This modified regimen was used as one of the available FEC-based options in the November 2006 fully recruited European Organisation for Research and Treatment of Cancer/p53 study. By the closure of the study, November 2006, 121 patients had been randomised to this regimen since 2002 and we have so far no reports of AML/MDS, although we have one report of a mantle cell lymphoma.

Another potential risk with higher doses of epirubicin is that of myocardial toxicity. We now have reports on clinical myocardial toxicity in 11 patients in the tailored and dose-escalated FEC arm and five in the marrow-supportive CTCb arm. We have previously reported in two substudies on patients from two of the participating sites in the SBG 9401 study, an increased risk for subclinical cardiac side-effects for the tailored FEC regimen using an anti-myosin monoclonal antibody and serum determination of N-terminal proatrial natriuretic peptide. The clinical side-effects have so far been limited [33, 34]. The so far relatively limited clinical cardiac side-effects, despite a median epirubicin dose of 780 mg/m² in the tailored FEC arm, may be related to epirubicin being given as a 1-h infusion. Some taxane and dose-dense studies have been demonstrated to improve OS compared with different anthracycline combinations, albeit that all comparator regimens may not have been optimal [7, 35, 36]. The first report has also been presented on sequential and dose-dense doxorubicin, paclitaxel and cyclophosphamide with and without marrow-supported high-dose therapy, demonstrating a nonsignificant trend in advantage for the non-high-dose arm [21].

In conclusion, the SBG 9401 study demonstrated no OS benefit by haematopoietic stem cell–supported high-dose therapy as adjuvant breast cancer therapy to patients with a high risk of relapse. Our data demonstrate the effectiveness of the tailored FEC regimen by reducing breast cancer relapses, but the outcome of this regimen versus dose-dense and taxane-based regimens is not known. We are presently exploring the possibility of a tailored EC strategy with docetaxel in sequence. The tailored FEC regimen, however, in this study needs modification in order to reduce the risk of AML/MDS and cardiac toxicity.

**acknowledgements**

The study was supported by grants from the Nordic Cancer Union, Swedish Cancer Society, Roche, Amgen and former Pharmacia and Upjohn. Data safety and monitoring committee: Lars Erik Rutqvist, Karolinska University Hospital and Institutet, Stockholm, Sweden; Eva Skovlund, University of Oslo, Oslo, Norway; JN, presently at Trial Form Support, Stockholm, Sweden.
References


appendix

Sweden

Jonas Bergh, Principal investigator and Nils Wilking, Coinvestigator, Radiumhemmet Karolinska Hospital, Stockholm; Henrik Lindman, Department of Oncology, University Hospital, Uppsala; Martin Höglund, Department of Hematology, University Hospital, Uppsala; Mats Bengtsson, Department of Clinical Immunology, University Hospital, Uppsala; Astrid Gruber, Department of Hematology, Karolinska Hospital, Stockholm; Tommy Fornander, Department of Oncology, Södersjukhuset, Stockholm; Per Ljungman, Department of Hematology, Huddinge Hospital, Stockholm; Dagny Petterson-Sköld, Department of Oncology, Danderyd Hospital, Stockholm; Nils-Olof Bengtsson, Department of Oncology University Hospital, Umeå; Eva Löfvenberg, Department of Hematology, University Hospital, Umeå; Kenneth Villman, Department of Oncology, Örebro Hospital, Örebro; Gustaf Söderlund, Department of Oncology, University Hospital, Linköping; Karin Karlsson, Department of Hematology, Sahlgrenska Hospital, Göteborg; Jan Mattson and Svante Jansson, Department of Surgery, Sahlgrenska Hospital, Göteborg; Inger Braide, Department of Hematology, Sahlgrenska Hospital, Göteborg; Göran Carlsson, Department of Oncology, Östra Hospital, Göteborg; Stig Rödier, Department of Hematology, Östra Hospital, Göteborg; Per Malmström, Department of Oncology, University Hospital, Lund; Bengt Sallerfors, Department of Hematology, University Hospital, Lund; Johan Ahlgren and Ann Gawelin, Department of Oncology, Gävle Hospital, Gävle; Martin Söderberg, Department of Oncology, Karlstad Hospital, Karlstad; Jörgen Hansen, Department of Oncology, Västerås Hospital, Västerås; Britta Stenstam, Department of Oncology, Målarsjukhuset, Eskilstuna; Jan-Henry Svensson, Målarsjukhuset Eskilstuna of Oncology, Borås Hospital, Borås; Bengt Norberg, Department of Oncology, Ryhov Hospital, Jönköping.

Norway

Bjørn Erikstein, The Norwegian Radiumhospital, Oslo; Harald Holte, Hematology section, The Norwegian Radiumhospital, Oslo; Gunnar Kvalheim, Department of Medicine, The Norwegian Radiumhospital, Oslo; Hilde Heen Sommer, Department of Oncology, Ullevål Hospital, Oslo; Jon Magnus Tangen, Department of Hematology, Ullevål Hospital, Oslo; Gun Anker, Department of Oncology, Haukeland Hospital, Bergen; Steinar Lundgren, Department of Oncology, Regional Hospital, Trondheim; Erik Wist, Department of Oncology, Regional Hospital, Tromsø.

Finland

Tom Wiklund and Carl Blomqvist, Department of Oncology, University Hospital, Helsinki; Eva Salminen, Department of Oncology, University Hospital, Turku; Kari Remes, Department of Internal Medicine, University Hospital, Turku; Marja Lehtinen and Elli Koivinen, Department of Clinical Chemistry/Division of Hematology, University Hospital, Tampere; Pirkko Kellokumpu-Lehtinen, Department of Oncology, University Hospital, Tampere; Taina Turpeenniemi-Hujanen and Outi Kuitinen, Department of Oncology, Oulu University Hospital; Leena Voutilainen, Department of Oncology, Kuopio University Hospital.

Denmark

Mansoor Raza Mirza and Carsten Rose, Department of Oncology, University Hospital, Odense.