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CLINICAL TRIAL

The potential risk of neoadjuvant chemotherapy in breast cancer patients—results from a prospective randomized trial of the Austrian Breast and Colorectal Cancer Study Group (ABCSG-07)

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Abstract *Purpose* To evaluate the impact that pre- and postoperatively administered chemotherapy with cyclophosphamide, methotrexate and fluorouracil (CMF) and postoperative chemotherapy vs. postoperative chemotherapy alone have on long-term prognosis. *Patients and Methods* The ABCSG conducted a nationwide randomized phase III trial in high-risk endocrine non-responsive breast cancer patients comparing pre- and postoperative chemotherapy containing CMF as preoperative treatment vs. postoperative chemotherapy alone between 1991 and 1999. From 1996 the ABCSG-07 protocol was amended to also allow randomization of high-risk endocrine-responsive patients. Of 423 eligible patients with high-risk primary breast cancer, 203 patients were randomly assigned to preoperatively receive three cycles of CMF (cyclophosphamide, methotrexate, fluorouracil; 600/40/600 mg/m^2) intravenously on day 1 and 8, while 195 patients received postoperative chemotherapy alone. In both groups, three cycles of CMF were given initially, and another three cycles of CMF were administered in node-negative patients, whereas node-positive patients received three cycles of EC (epirubicin, cyclophosphamide; 70/600 mg/m^2). *Results* Overall response rate to preoperative chemotherapy with three cycles of CMF was 56.2%; complete pathological response was achieved in 12 patients (5.9%). Recurrence-free survival was significantly better in patients receiving chemotherapy postoperatively (HR 0.7, 0.515–0.955; $P = 0.024$). No survival difference was observed between the two therapy groups (HR 0.800, 0.563–1.136; $P = 0.213$). *Discussion* Preoperative chemotherapy with CMF has to be considered as insufficient in high-risk breast cancer patients. Delayed surgery and anthracycline-based chemotherapy result in shorter recurrence-free survival but not overall survival.

Keywords Preoperative chemotherapy · Breast cancer · CMF · EC · Postoperative chemotherapy · Response

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Introduction

Neoadjuvant (preoperative) chemotherapy is the standard treatment for locally advanced breast cancer and in many centers is considered a valid option for primary operable disease.

Several potential advantages over the traditional strategy of surgery followed by adjuvant chemotherapy have been reported in the past 20 years [1–3]. Preoperative chemotherapy reduces the size of the primary tumor and of lymph node metastases in more than 80% of cases, offering the option of breast-conserving surgery for the majority of these patients [4–6]. Moreover, sequencing the schedule of chemotherapy before surgery theoretically permits the response of the primary tumor to a particular chemotherapy regimen to be assessed. This "in vivo" assessment could provide the opportunity to adjust chemotherapy pending on response to the initial treatment regimen.

One of the initial reasons for exploring neoadjuvant chemotherapy in breast cancer patients was to investigate whether delivery of chemotherapy prior to surgery would improve survival in patients with locally advanced breast carcinoma. The hypothesis was that early administration of chemotherapy, when the micrometastatic tumor burden is minimal, would improve outcome as compared with only adjuvant chemotherapy after surgery. Preclinical animal studies have indicated that removal of the primary tumor could speed the growth rate of existing micrometastases [7].

The plurality of theoretical advantages of preoperative chemotherapy gave rise to substantial enthusiasm in the early nineties, but had to be proven. Therefore, the Austrian Breast and Colorectal Cancer Study Group (ABCSG) conducted a nationwide prospective randomized trial comparing pre- and postoperative chemotherapy vs. postoperative chemotherapy alone starting in 1991. Meanwhile, several clinical trials could not confirm the expected long-term survival benefit for preoperative chemotherapy [5, 8].

The majority of so far published data are derived from highly effective chemotherapeutic agents, i.e., taxanes and anthracyclines. The early start of our trial is the reason why an "old-fashioned" CMF regimen was administered. This, however, provides the opportunity to investigate what could happen when using chemotherapy regimes that must be deemed insufficient from today's perspective.

Patients and methods

Patient selection

Between 1991 and 1999, 429 patients with core needle biopsy-proven primary breast cancer were randomized in the ABCSG-07 trial comparing pre- and postoperative chemotherapy vs. postoperative chemotherapy alone. Thirty-one patients failed to meet the inclusion criteria or were not compliant. Thus, a total number of 398 patients remained in the final analysis: 203 patients were treated pre- and postoperatively, while 195 patients received postoperative chemotherapy only. Women who had primary operable receptor-negative breast cancer diagnosed by core needle biopsy were eligible. The main inclusion criterion was core needle biopsy-proven breast cancer and/or positive lymph nodes (clinically and/or radiologically) and receptor negativity. Within the first 5 years of randomization inclusion in the trial was restricted to patients presenting with hormone receptor-negative tumors. From 1996, a protocol amendment allowed recruitment of high-risk hormone receptor-positive patients. Those patients with clinically nodal-positive disease were defined as high-risk patients.

Patients with breast cancer clinically staged T1-3, N0 or N1 and M0 were enrolled. The basic staging procedures included chest X-ray, liver ultrasound and bone scan to detect distant metastases. Patients with inflammatory breast cancer or distant metastases were not eligible for this trial.

At each participating institution the local ethics committee approved the trial. All patients had to give written informed consent to enter the study.

ABCSG-07 trial design

Trial design is given in Fig. 1. In the preoperative therapy group three cycles of CMF were administered prior to surgery. In the postoperative therapy group all patients were initially treated with three cycles of CMF. In both groups, those patients presenting with histologically proven node-negative disease received another three cycles of CMF, while node-positive breast cancer patients subsequently received three cycles of EC.

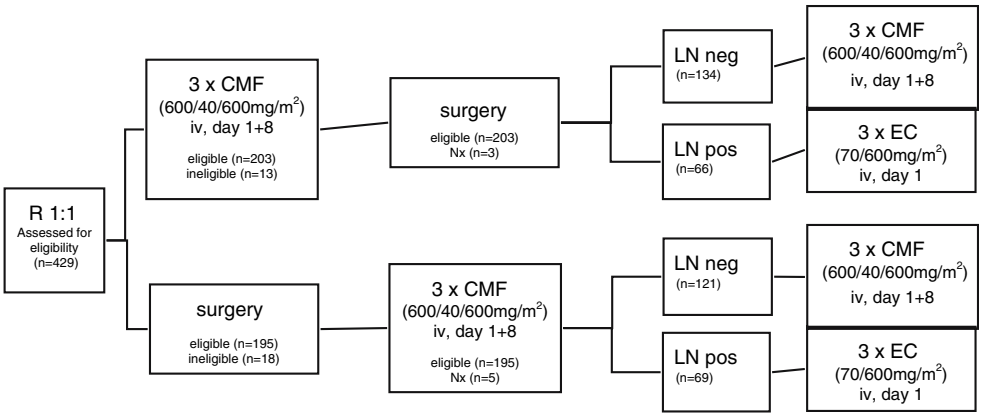
Treatment regimen

All patients in the preoperative therapy group ($n = 203$) received three cycles of CMF; cyclophosphamide 600 mg/m^2, methotrexate 40 mg/m^2 and fluorouracil 600 mg/m^2 intravenously (iv) on days 1 and 8, every 3 weeks. Node-positive patients received the anthracycline-based chemotherapy regimen EC: epirubicin 70 mg/m^2 and cyclophosphamide 600 mg/m^2 on day 1, every 3 weeks.

Assessment of response

Response was evaluated clinically, radiologically and histologically. Complete pathological response was defined as

Fig. 1 Trial design



R = randomization, CMF = cyclophosphamide, methothrexat, fluorouracil, LN = lymph node, EC = epirubicin, cyclophosphamide

complete disappearance of invasive breast cancer in the final histological specimen of the primary tumor. Partial response was a reduction of more than 50% in the initial tumor size; stable disease was a reduction of less than 50%, and progressive disease was any increase in tumor size after chemotherapy.

Surgery

The surgical procedure was breast-conserving surgery or modified radical mastectomy, both including axillary dissection in all patients. Histologically clear margins were mandatory. All patients received radiotherapy after breast-conserving therapy. After mastectomy, radiotherapy was administered at the discretion of the treating physician and the patient.

Statistical analysis

Patient characteristics are tabulated by treatment group. Median follow-up time was calculated as the median observation time among all patients. Survival and disease-free interval were estimated with the Kaplan–Meier method, and the log rank statistic was used to test for differences between groups.

Results

Patient characteristics are listed in Tables 1, 2. Both groups were well balanced for age, tumor size, nodal status and hormone receptor status. Median age in the preoperative group was 50.3 and 51.5 years in the postoperative therapy group. In both groups, nearly half of the patients were premenopausal at time of randomization, namely 100 (49.3%) and 97 (49.7%) patients; of these 23 (11.3%) and 27 (13.8%) were younger than 40 years. The vast majority of enrolled patients had hormone receptor-negative breast cancer, namely 89.2% ER-negative tumors in the preoperative group and 84.1% in the postoperative group, 77.8 and 79% PR-negative. This patient selection is the result of the protocol, which allowed only hormone receptor-negative patients in the first 5 years of recruitment.

Response to primary chemotherapy

Clinical and radiological response evaluation was performed prior to surgery. Palpation of the breast mass in two dimensions and mammography were mandatory after preoperative administration of three cycles CMF. The median clinical size of the primary tumor was 2 cm (range 1–8 cm) at time of surgery. The results of clinical, radiological and histological response rates are shown in Table 3.

Clinical evaluation of response to primary chemotherapy resulted in a slight overestimation of tumor shrinkage, whereas radiological evaluation was more or less the same as histological tumor response.

We did not observe any measurable trend to a down-staging of lymph node involvement after primary chemotherapy with CMF. The mean number of positive nodes was 2.47 (1–27) and 2.29 (1–23) in the two trial arms ($P = 0.6$). Ninety-two (45.3%) and 102 (50.3%) patients had negative lymph nodes in the preoperative and post-operative therapy groups, respectively.

Adjuvant chemotherapy

According to the ABCSG-07 protocol, all patients with positive nodes at time of surgery received three cycles of an anthracycline-based adjuvant chemotherapy. Three

Table 1 Patients characteristics

Characteristics	$n = 398$	
Age, years	Pre- and postop therapy $n = 203$ (%)	Postop therapy $n = 195$ (%)
Median	50.3	51.5
Range	29–71	28–70
<50 years	97 (47.8)	90 (46.2)
>50 years	106 (52.2)	105 (53.8)
Menopause		
Premenopausal	100 (49.3)	97 (49.7)
Postmenopausal	103 (50.7)	98 (50.3)
Histology		
Ductal	159 (78.3)	167 (85.7)
Lobular	17 (8.4)	23 (11.8)
Others	27 (13.3)	5 (2.5)
Tumor size, pT		
pT1	45 (22.2)	52 (26.7)
pT2	136 (67.0)	121 (62.1)
pT3	18 (8.9)	17 (8.7)
pTx	4 (1.9)	
No statistical significant difference between the study arms regarding tumor size. $P = 0.37$		
Nodes (at time of randomization)		
Negative	134 (66.0)	121 (62.0)
Positive	66 (32.5)	69 (35.4)
Nx	3 (1.5)	5 (2.6)
ER		
Negative	181 (89.2)	164 (84.1)
Positive	19 (9.4)	17 (8.7)
Unknown	3 (1.4)	14 (7.2)
PR		
Negative	158 (77.8)	154 (79.0)
Positive	36 (17.7)	25 (12.8)
Unknown	9 (4.5)	16 (8.2)
No statistical significant difference between the study arms regarding hormone receptor. $P = 0.97$		

ER, estrogen receptor; PR, progesterone receptor; pos, positive

cycles of EC were given in 98 patients (48.3%) in the preoperative therapy group immediately after surgery, while 77 patients (39.5%) in the postoperative therapy group received EC after completion of three cycles of CMF.

Surgery

Patients who received preoperative therapy had a slightly better likelihood of undergoing breast-conserving surgery, namely 133 vs. 116 (65.5% vs. 59.5%). However, the difference was not statistically significant ($P = 0.25$).

Survival analysis

We observed a total number of 165 recurrences (local recurrences and distant metastases) in 149 patients after a median follow-up of 9 years. The rate of local recurrences was similar in both groups: 27 patients (13.3%) in the preoperative and 16 patients (8.2%) in the postoperative treatment group ($P = 0.1$). Distant metastases were observed in 62 (30.5%) and 44 (22.6%) patients ($P = 0.07$).

Univariate analysis of recurrence-free survival revealed a significant benefit for the postoperative treatment group (HR 0.7; 0.515–0.955; $P = 0.024$), see Fig. 2. Multivariate analysis including therapy arm, estrogen receptor and tumor size determined therapy arm as independent significant factor.

In contrast, overall survival was not affected by therapy group, HR 0.800, 0.563–1.136; $P = 0.213$. Patients who responded with complete pathological or partial response experienced significant fewer recurrences, namely 48 events in 114 patients with pCR and PR, and 27 events in 47 patients who did not respond to preoperative chemotherapy ($P = 0.005$). Similar differences in outcome between responders and non-responders were seen for survival, 34 events in 114 patients who responded very well, and 23 events in 47 patients who did not respond ($P = 0.0039$) (Fig. 3).

Toxicity

No significant differences in toxicity were observed between the therapy groups. The majority of chemotherapy side-effects were classified WHO grade 1. The most serious chemotherapy-induced toxicity is illustrated in Table 4. No WHO grade 4 and only very few WHO grade 3 events were observed for diarrhea (1% WHO grade 3), stomatitis (2% WHO grade 3), neurological symptoms (no WHO grade 3 or 4 events), pulmonary toxicity (no WHO

Table 2 Multivariate Cox regression model for recurrence free survival

Variable	Standard-deviation	Chi-Quadrat	*P*-value	Hazard-ratio	95% Confidence interval	
Trial arm	0.16398	5.0611	0.0245	0.691	0.501	0.954
ER	0.26716	0.0088	0.9253	0.975	0.578	1.646
Tumor size	0.15090	2.9301	0.0869	1.295	0.963	1.740

ER, estrogen receptor

Table 3 Response to primary chemotherapy

Response	Clinical (%)	Radiological (%)	Histological (%)
$n = 203$			
CR/pCR	25 (12.3)	15 (7.3)	12 (5.9)
PR	102 (50.3)	102 (50.3)	102 (50.3)
SD	46 (22.7)	46 (22.7)	46 (22.7)
PD	1 (0.5)	2 (1.0)	1 (0.5)
Not done	29 (14.3)	38 (18.7)	42 (20.6)
CR + PR	127 (62.6)	117 (57.6)	114 (56.2)

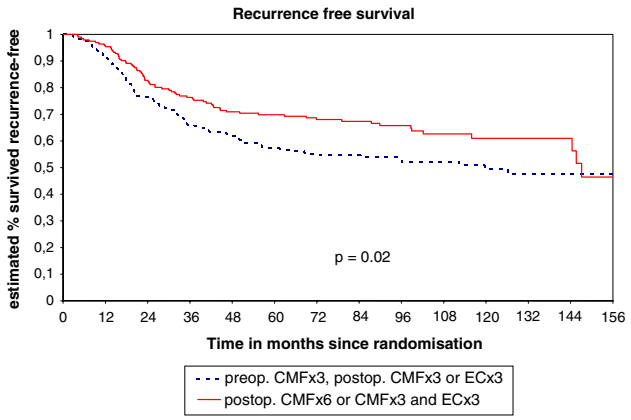


Fig. 2 Recurrence-free survival

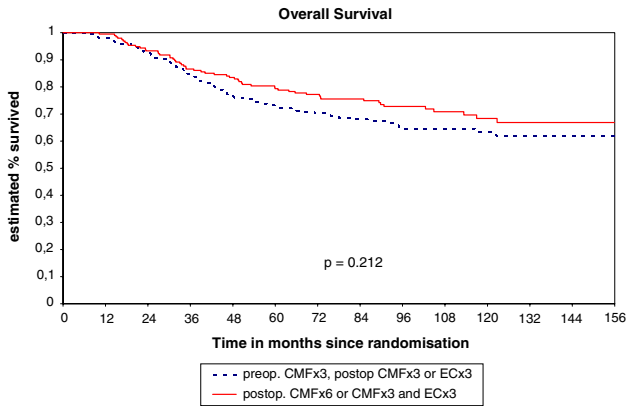


Fig. 3 Overall survival

grade 3 or 4 events), pain (2% WHO grade 3), cardiac events (1% WHO grade 3), impaired consciousness (no WHO grade 3 or 4 events).

Discussion

The ABCSG-07 trial investigated the role of pre- and postoperative chemotherapy containing CMF as preoperative treatment vs. postoperative chemotherapy alone in breast cancer patients. The primary aim of the study was to investigate any difference in overall and recurrence-free survival. Our findings do not support the hypothesis that preoperative chemotherapy with CMF prolongs overall survival (HR 0.800, $P = 0.213$). Furthermore, our data suggest a significantly increased recurrence-free survival in patients treated with postoperative chemotherapy alone, containing three cycles of EC in node positive patients (HR 0.700, $P = 0.02$). To our knowledge, this is the first prospective randomized trial indicating a potential drawback in terms of recurrence-free survival following preoperative administration of chemotherapy.

As recently confirmed by a meta-analysis of nine randomized trials covering 3,946 patients, all randomized trials of preoperative chemotherapy vs. standard adjuvant therapy showed an equivalent efficacy in terms of survival [9, 10]. No difference was observed between pre- and postoperative chemotherapy groups with regard to death, disease progression or distant recurrences. The largest of these studies is the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18 which randomized 1,523 patients to receive four cycles of doxorubicin and cyclophosphamide (AC) given either before or after surgery. At the 9-year follow-up, no difference was seen between neoadjuvant and adjuvant chemotherapy in terms of DFS (55 vs. 50%, ns) [4].

Another large trial conducted by Gianni et al. randomized 1,355 patients with breast cancer >2 cm to three groups: adjuvant doxorubicin (A) followed by cyclophosphamide, methotrexate, and 5-FU (CMF); adjuvant doxorubicin and paclitaxel (AC) followed by CMF, and neoadjuvant AT followed by CMF. At the 5-year of follow-up, adjuvant chemotherapy was similar to preoperative chemotherapy in terms of DFS ($P = 0.24$) and OS ($P = 0.81$) [11].

Other smaller randomized phase III trials of neoadjuvant vs. adjuvant chemotherapy used different chemotherapy combinations and did not observe any survival benefit for the neoadjuvant group [8, 12–14]. In nearly all trials an anthracycline-containing regimen was administered either before or after surgery. Trials starting in the late nineties even used taxanes in the preoperative setting without any benefit in terms of outcome [15, 16]. The addition of taxanes preoperatively decreased the incidence of local recurrence, improved DFS in patients with a clinical partial response after AC and did not affect OS [17]. In contrast to the published data, ABCSG-07 indicated a significant outcome difference between the therapy groups.

We may only speculate about the underlying mechanism that decreased recurrence-free survival in the preoperative CMF therapy group:

1. Chemotherapy regimen. The early onset of our trial may be considered an important issue in a trial design

Table 4 Toxicity

	Pre- and postoperative chemotherapy ($n = 203$)	Postoperative chemotherapy ($n = 195$)	Statistical comparison between therapy groups (Wilcoxon test)
Nausea/vomitus			$P = 0.06$
WHO grade 1	75 (36.9%)	68 (34.9%)	
WHO grade 2	64 (31.5%)	53 (27.1%)	
WHO grade 3	24 (11.8%)	18 (9.2%)	
WHO grade 4	0	0	
Leucopenia			$P = 0.62$
WHO grade 1	36 (17.7%)	33 (16.9%)	
WHO grade 2	40 (19.7%)	43 (22.1%)	
WHO grade 3	21 (10.3%)	22 (11.3%)	
WHO grade 4	6 (2.9%)	4 (2.1%)	
Infection/fever			$P = 0.89$
WHO grade 1	17 (8.3%)	13 (6.6%)	
WHO grade 2	14 (6.9%)	13 (6.6%)	
WHO grade 3	0	2 (1.0%)	
WHO grade 4	0	0	
Thrombopenia			$P = 0.65$
WHO grade 1	15 (7.4%)	12 (6.2%)	
WHO grade 2	4 (2.0%)	3 (1.5%)	
WHO grade 3	3 (1.5%)	2 (1.0%)	
WHO grade 4	1 (0.5%)	2 (1.0%)	
Alopecia			$P = 0.37$
WHO grade 1	45 (22.2%)	43 (22.1%)	
WHO grade 2	32 (15.8%)	33 (16.9%)	
WHO grade 3	33 (16.2%)	25 (12.8%)	
WHO grade 4	5 (2.5%)	2 (1.0%)	

using a chemotherapy regimen without an anthracycline or taxane. Nowadays CMF cannot be considered as sufficient adjuvant therapy for high-risk breast cancer patients. Thus, the efficacy of cytotoxic agents administered preoperatively in breast cancer patients needs to be considered crucial in terms of recurrence-free survival. CMF pretreatment might allow the development of chemotherapy-resistant clones.

2. Duration of preoperative therapy. Beyond the issue of inappropriate cytotoxic agents, our results may be caused by the duration of preoperative therapy. Recent data suggest that longer treatment compares favorably with shorter treatment regardless of the type of therapy (chemotherapy or endocrine therapy) [16, 18]. Kaufmann et al. recommend at least four cycles of chemotherapy preoperatively [19]. We administered three cycles of CMF preoperatively in all patients in the preoperative therapy group, which must be considered insufficient.
3. Response rate: Another aspect of our trial results that is very closely associated with outcome is the response rate. We achieved an overall response rate of 56.2% histologically and a complete pathological response (pCR) rate of 5.9% when using preoperative chemotherapy with CMF. In fact, pCR achievement may produce a better outcome, probably because the micrometastatic disease was eradicated. Data recently presented by the National Surgical Adjuvant Breast and Bowel Project-B27 show that, despite an increase in pCR rate for the sequential AC-docetaxel (AC-D) arm vs. AC alone, there was as yet no survival advantage [15]. The same study confirmed the favorable prognosis in patients who achieved pCR, irrespectively of the regimen used. The relatively small percentage of patients who achieved pCR (12.8–14.3% for AC vs. 26.1% for AC-D), the concomitant administration of tamoxifen, and the limited number of events might have contributed to obscuring the superiority of AC-D.

However, the efficacy and modality of systemic treatment administered preoperatively substantially affect the pCR rate. Neoadjuvant endocrine therapy produces pCR rates ranging between 1 and 8% [20–23]. Hence, response

rates achieved in our study are more likely to be compared to those achieved with preoperative endocrine therapy in hormone receptor-positive patients. In contrast to neoadjuvant endocrine therapy, which is given exclusively to hormone-responsive patients, an appropriate predictive marker for CMF therapy is lacking. Up to now, the literature contains no clear information on effect on prognosis following neoadjuvant endocrine therapy. The published trials report overall response rates of up to 55% [20] and increased breast-conserving rates of up to 44% [21].

At this stage, our results indicating a clear disadvantage with respect to recurrence-free survival in the preoperative therapy group require careful consideration. Although our study results are weakened by several factors, namely recruitment time of more than 9 years, inhomogeneous patient selection and insufficient chemotherapy from today's perspective, we achieved a treatment effect in mainly hormone-unresponsive patients that is similar to the effect achieved with endocrine therapy in hormone-responsive patients. However, minimally effective preoperative therapy may potentially harm our patients.

Several studies have been conducted with the aim of identifying predictive markers of pCR. Poorly differentiated tumors with a high proliferation rate and without expression of hormone receptors are more chemosensitive and are associated with a higher rate of pCR [6, 24, 25]. However, the prognostic value of achieving pCR is associated with better outcome irrespective of hormone receptor status [26].

Overall, current knowledge does not suffice to differentiate patients at various degrees of risk and does not allow for an individualized choice of therapy. In conclusion, this analysis conducted in nearly 400 patients with hormone receptor-negative breast cancer shows the slight efficacy of preoperative chemotherapy with CMF to be comparable to that of endocrine treatment in hormone-responsive breast cancer. Outcome is not affected substantially by preoperative chemotherapy with CMF. Therefore, preoperative administration of CMF may be considered in patients in whom more aggressive treatment regimens are not applicable and tailored therapy is not available or possible for several reasons.

Appendix

Apart from the authors of this Manuscript, members of the Austrian Breast and Colorectal Cancer Study Group participating in Trial 7 included the following: M. Schmidinger (Departments of Surgery and Internal Medicine, Vienna University, Vienna); M. Stierer, H. Spoula (Department of Surgery, Hanusch Hospital, Vienna); K. Renner (Department of Surgery, Donau-Hospital SMZ-Ost, Vienna); F. Hofbauer, M. Lang, D. Bauer (Department of Surgery, Oberpullendorf Hospital, Oberpullendorf); O. Langer (Department of Surgery, Oberwart Hospital, Oberwart); W. Döller, E. Melbinger-Zeinitzer and E. Schrofler (Department of Surgery and Lymphology, Wolfsberg Hospital, Wolfsberg); K. Haider and A. Lenauer (Department of Surgery, Wiener Neustadt Hospital, Wiener Neustadt); C. Baldinger, P. Oppitz and S. Pillichshammer (4. Internal Department, Kreuzschwestern Wels Hospital, Wels); H. Hausmaninger, B. Mlineritsch (Third Medical Department, Salzburg Hospital, Salzburg); P. Steindorfer, M. Smola, G. Rosanelli, L. Kronberger and C. Bauer (Department of Surgery and Internal Medicine, Graz University, Graz Hospital, Graz); H. Stadler (Department of Surgery, Knittelfeld Hospital, Knittelfeld); G. Luschin-Ebengreuth, I. Thiel (Department of Gynecology, Graz University, Graz); E. Kubista, (Division of Special Gynecology, Vienna University, Vienna); R. Schildberger, F. Kugler and R. Klug (Department of Surgery, BHS Hospital, Linz); H. Trapl (Department of Surgery, Thermenklinikum, Baden).

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