original article

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Adverse prognostic value of peritumoral vascular invasion: is it abrogated by adequate endocrine adjuvant therapy? Results from two International Breast Cancer Study Group randomized trials of chemoendocrine adjuvant therapy for early breast cancer

G. Viale[1]*, A. Giobbie-Hurder[2], B. A. Gusterson[3], E. Maiorano[4], M. G. Mastropasqua[1], A. Sonzogni[1], E. Mallon[3], M. Colleoni[5], M. Castiglione-Gertsch[6], M. M. Regan[7], K. N. Price[8], R. W. Brown[9], R. Golouh[10], D. Crivellari[11], P. Karlsson[12], C. Öhlschlegel[13], R. D. Gelber[14], A. Goldhirsch[15,16] & A. S. Coates[17,18]

[1]Division of Pathology and Laboratory Medicine, European Institute of Oncology, University of Milan, Milan, Italy; [2]International Breast Cancer Study Group, Statistical Center, Dana-Farber Cancer Institute, Boston, MA, USA; [3]Division of Cancer Sciences and Molecular Pathology, Faculty of Medicine, University of Glasgow, Glasgow, UK; [4]Department of Pathological Anatomy, University of Bari, Bari, Italy; [5]Department of Medicine, Research Unit in Medical Senology, European Institute of Oncology, Milan, Italy; [6]International Breast Cancer Study Group Coordinating Center, Bern, Switzerland; [7]International Breast Cancer Study Group, Statistical Center, Dana-Farber Cancer Institute, Harvard School of Public Health, Boston, MA, USA; [8]International Breast Cancer Study Group, Statistical Center, Frontier Science and Technology Research Foundation, Boston, MA, USA; [9]Melbourne Pathology, Collingwood, Victoria, Australia; [10]Department of Pathology, Institute of Oncology, Ljubljana, Slovenia; [11]Department of Medical Oncology, Centro di Riferimento Oncologico, Aviano, Italy; [12]Department of Oncology, Sahlgrenska University Hospital, Gothenburg, Sweden; [13]Swiss Group for Clinical Cancer Research (SAKK), Bern, Switzerland; [14]International Breast Cancer Study Group, Statistical Center, Dana-Farber Cancer Institute, Frontier Science and Technology Research Foundation, Harvard School of Public Health, Boston, MA, USA; [15]European Institute of Oncology, Milan, Italy; [16]Department of Medicine, Oncology Institute of Southern Switzerland, Bellinzona, Switzerland; [17]Scientific Committee, International Breast Cancer Study Group, Bern, Switzerland and [18]School of Public Health, University of Sydney, Sydney, Australia

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Background: Peritumoral vascular invasion (PVI) may assist in assigning optimal adjuvant systemic therapy for women with early breast cancer.

Patients and methods: Patients participated in two International Breast Cancer Study Group randomized trials testing chemoendocrine adjuvant therapies in premenopausal (trial VIII) or postmenopausal (trial IX) node-negative breast cancer. PVI was assessed by institutional pathologists and/or central review on hematoxylin–eosin-stained slides in 99% of patients (analysis cohort 2754 patients, median follow-up >9 years).

Results: PVI, present in 23% of the tumors, was associated with higher grade tumors and larger tumor size (trial IX only). Presence of PVI increased locoregional and distant recurrence and was significantly associated with poorer disease-free survival. The adverse prognostic impact of PVI in trial VIII was limited to premenopausal patients with endocrine-responsive tumors randomized to therapies not containing goserelin, and conversely the beneficial effect of goserelin was limited to patients whose tumors showed PVI. In trial IX, all patients received tamoxifen: the adverse prognostic impact of PVI was limited to patients with receptor-negative tumors regardless of chemotherapy.

Conclusion: Adequate endocrine adjuvant therapy appears to abrogate the adverse impact of PVI in node-negative disease, while PVI may identify patients who will benefit particularly from adjuvant therapy.

Key words: adjuvant therapy, breast cancer, endocrine responsiveness, metastasis, prognosis, vascular invasion

introduction

Metastasis is a crucial feature of malignancy. In most cases, an early metastatic event is the invasion of lymphatic or blood vessels. Detection of such vascular invasion in patients with early breast cancer has been observed by our own group [1–3] and others [4–9] to be an adverse prognostic factor in breast cancer. Similar findings have been reported in other cancer types [10–13]. In patients with axillary node-negative breast cancer, vascular invasion may be a marker of occult nodal metastasis [14, 15] or of the risk of direct hematogenous spread.

*Correspondence to: Prof. G. Viale, Department of Pathology, European Institute of Oncology, Via Ripamonti 435, 20141 Milan, Italy; Tel: +39 (02) 5748 9419; Fax: +39 (02) 5748 9417; E-mail: giuseppe.viale@ieo.it

In the present study, we examine the prognostic significance of peritumoral vascular invasion (PVI) in two randomized controlled trials conducted by the International Breast Cancer Study Group (IBCSG) in patients with node-negative breast cancer. In particular, we find that the adverse prognostic effect of PVI is not seen among patients assigned what is now regarded as adequate endocrine therapy. Evaluation of prognostic factors such as PVI, in the context of clinical trials, has the advantage that treatment allocation is unbiased, and follow-up and reporting are likely to be more standardized than in non-trial series.

patients and methods

IBCSG trials VIII and IX

Patients were treated in one of two IBCSG randomized clinical trials, which have been described in detail elsewhere [16, 17]. Briefly, from March 1990 through October 1999, IBCSG trial VIII [16] randomly assigned 1109 premenopausal or perimenopausal breast cancer patients with node-negative disease to receive one of four treatments: (i) no adjuvant systemic treatment; (ii) goserelin (3.6 mg s.c. implants monthly) for 24 months; (iii) six 28-day courses of 'classical' cyclophosphamide, methotrexate and 5-fluorouracil (CMF) or (iv) six courses of classical CMF followed by 18-monthly doses of goserelin. Systemic adjuvant therapy was to begin within 6 weeks of primary surgery. In April 1992, on the basis of results from other trials, randomization to the no adjuvant treatment control arm was discontinued after enrolling a total of 205 patients, 46 of them to the control arm. From October 1988 to August 1999, IBCSG trial IX [17] randomly assigned 1669 eligible and assessable postmenopausal breast cancer patients with node-negative disease to receive one of two adjuvant therapy regimens: tamoxifen 20 mg daily for 5 years or three cycles of classical CMF followed by tamoxifen 20 mg daily for 57 months.

In both trials, patients with estrogen receptor (ER)-positive, ER-negative and ER-unknown tumors (ER-unknown status allowed only if ER determination was not possible because of lack of tumor material) were eligible until 1998; at that time, protocol amendments restricted enrollment to patients with ER-positive tumors. Over 94% of patients were randomized before the amendments' release. Institutional review boards reviewed and approved the protocols, and informed consent was required according to the criteria established within the individual countries.

vascular invasion

In these trials, PVI was requested as part of the routine pathological work-up at study entry and at central pathology review of a hematoxylin and eosin section using criteria previously described [1]. PVI was defined as the presence of tumor cell emboli within a vessel space, which were identified by associated fibrin clot and/or an endothelial cell lining. The study protocol required that at least two sections of primary tumor be taken at right angles to one another to include the interface of the growing tumor border and the adjacent breast tissue. Generally, ~6 cm^2 of breast tissue immediately adjacent to the primary tumor, but within 1 cm of the tumor border, was available for the assessment of PVI. Routine hematoxylin and eosin sections were used, and blood and lymphatic vessel invasion was not distinguished.

PVI was recorded as present, absent or not done at both local and central assessments (Table 1). For this analysis, we have defined PVI as 'present' if PVI was assessed as present by either the local pathologist or the central reviewer and 'absent' otherwise. The 24 cases not examined by either local pathologist or central reviewer are not included in the analysis cohort.

classification of hormone receptor status

Presence or absence of ER and progesterone receptor (PgR) was determined from central review [18] when available (82% of cases), with presence defined as ≥1% immunoreactive cells. The remainder were classified based on local assessment using immunohistochemistry when available or ligand-binding assay results otherwise [18]. In trial VIII, tumors were considered hormone receptor present if one or both of ER or PgR was present and were classified as hormone receptor absent if ER was absent and PgR was either absent or unknown. In trial IX, hormone receptor status was based on ER only. In both trials, if the ER status of the tumor was unknown, hormone receptor status was classified as unknown, and these 24 patients were not included in analyses using hormone receptor status.

assessment of 'adequate' adjuvant therapy

Since these trials were designed, evidence has emerged that premenopausal patients with hormone receptor-positive tumors are not adequately treated by chemotherapy alone, as was common in the 1990s [19]. For trial VIII, therefore, adequate treatment of patients having tumors expressing hormone receptors was defined as treatment including the gonadotropin-releasing hormone analogue goserelin; among patients with hormone receptor-absent tumors, treatment with chemotherapy was considered adequate. Similarly, in the light of our own [17] and other [20] data, adequate therapy for patients in trial IX whose tumors did not express hormone receptors was defined as including CMF chemotherapy.

statistical methods

The two trials were analyzed separately. The association of presence of PVI with clinical and pathological features was assessed using Fisher's exact tests. Disease-free survival (DFS) was defined in the trials [16, 17] as the length of time from the date of randomization to any relapse (including ipsilateral breast recurrence, contralateral breast cancer and distant recurrence), second primary malignancy, or death, whichever occurred first. The distribution of DFS was summarized using the Kaplan–Meier method [21]. Proportional hazards regression [22] was used to investigate the associations of PVI and other factors with DFS and estimate hazard ratios (HRs).

In exploratory analyses of the relation of PVI and adequate adjuvant therapy with DFS, for trial VIII the following groups were considered: goserelin containing (goserelin or CMF → goserelin) or not (no treatment

Table 1. PVI as reported by local pathology and by central pathology review

PVI	Trial VIII (premenopausal; $N = 1109$)			Trial IX (postmenopausal; $N = 1669$)		
	Local, *n* (%)	Central, *n* (%)	Overall[a], *n* (%)	Local, *n* (%)	Central, *n* (%)	Overall[a], *n* (%)
Absent	875 (79)	829 (75)	832 (75)	1268 (76)	1284 (77)	1283 (77)
Present	168 (15)	180 (16)	264 (24)	244 (15)	232 (14)	375 (22)
Not examined	66 (6)	100 (9)	13 (1)	157 (9)	153 (9)	11 (1)

[a]The 'overall' proportion is classified as 'present' if PVI was noted by either the local pathologist or during central pathology review.
PVI, peritumoral vascular invasion.

or CMF) among hormone receptor-expressing tumors and CMF containing (CMF or CMF → goserelin) or not (goserelin or no treatment) among hormone receptor-absent tumors.

Cumulative incidence of locoregional failure and of distant recurrence (including contralateral breast event) was estimated in the presence of 'other' events (second primary cancer and death without recurrence) and assessed using Gray's test [23].

Median follow-up at the time of analysis was 9.8 years for trial VIII and 10.9 years for trial IX.

results

Of 2778 patients, 2754 (99%) had PVI assessment available and represent the analysis cohort. PVI was present in 264

Table 2. Association of PVI with other clinical and pathological characteristics

	Trial VIII (premenopausal)				Trial IX (postmenopausal)			
	Vascular invasion				Vascular invasion			
	Absent		Present		Absent		Present	
	n	%[a]	*n*	%[a]	*n*	%[a]	*n*	%[a]
All patients	832		264		1283		375	
Age at randomization								
≤39	160	19.2	56	21.2	1	0.1	–	–
40–49	527	63.3	166	62.9	22	1.7	13	3.5
50–59	145	17.4	42	15.9	536	41.8	163	43.5
≥60	–	–	–	–	724	56.4	199	53.1
Local treatment								
Mastectomy	355	42.7	128	48.5	629	49.0	194	51.7
BCS with RT	431	51.8	122	46.2	574	44.7	163	43.5
BCS without RT	46	5.5	14	5.3	80	6.2	18	4.8
Treatment assignment								
No treatment	34	4.1	12	4.5	–	–	–	–
Goserelin × 24	265	31.9	77	29.2				
CMF × 6	258	31.0	96	36.4	–	–	–	–
CMF × 6 → goserelin × 18	275	33.1	79	29.9	–	–	–	–
Tamoxifen	–	–	–	–	656	51.1	185	49.3
CMF → tamoxifen	–	–	–	–	627	48.9	190	50.7
ER status								
Absent	164	19.7	48	18.2	214	16.7	76	20.3
Present	661	79.4	216	81.8	1048	81.7	297	79.2
Unknown	7	0.8	–	–	21	1.6	2	0.5
PgR status								
Absent	193	23.2	57	21.6	367	28.6	124	33.1
Present	623	74.9	197	74.6	867	67.6	243	64.8
Unknown	16	1.9	10	3.8	49	3.8	8	2.1
Hormone receptor status								
Absent	144	17.3	46	17.4	214	16.7	76	20.3
Present	681	81.9	218	82.6	1048	81.7	297	79.2
Unknown	7	0.6	–	–	21	1.6	2	0.5
Tumor size[b]								
≤2 cm	521	62.6	153	58.0	786	61.3	198	52.8
>2 cm	302	36.3	108	40.9	459	35.8	173	46.1
Unknown	9	1.1	3	1.1	38	3.0	4	1.1
Tumor grade[c]								
1	162	19.5	31	11.7	257	20.0	34	9.1
2	360	43.3	122	46.2	530	41.3	164	43.7
3	297	35.7	110	41.7	415	32.3	171	45.6
Unknown	13	1.6	1	0.4	81	6.3	6	1.6

[a]Column percentages.

[b]In trial IX, the association of larger tumors with presence of PVI was significant: $P < 0.0001$.

[c]In each trial, this association was significant, trial VIII: $P = 0.008$ and trial IX: $P < 0.0001$.

All other associations in Table 2 were not statistically significant (Fisher's exact tests).

PVI, peritumoral vascular invasion; BCS, breast-conserving surgery; RT, adjuvant radiotherapy; CMF, cyclophosphamide, methotrexate and 5-fluorouracil chemotherapy; ER, estrogen receptor; PgR, progesterone receptor (trial VIII hormone receptor status is based on ER and PgR status and in trial IX, ER status only).

premenopausal patients' tumors (23.8%) in trial VIII and 375 postmenopausal patients' tumors (22.5%) in trial IX (Table 1).

associations of PVI with clinical and pathological factors

In univariate analyses, we found an association between the presence of PVI and higher tumor grade both in trial VIII ($P = 0.008$) and trial IX ($P < 0.0001$). Among postmenopausal patients in trial IX, the presence of PVI was also associated with larger tumor size ($P < 0.0001$). Other associations with clinical and pathological factors were not statistically significant (Table 2).

locoregional failure and distant recurrence

The presence of PVI significantly increased the cumulative incidence of both locoregional failure and distant recurrence among premenopausal patients (trial VIII; $P = 0.001$ and $P = 0.04$, respectively), where the difference in locoregional failure became evident 1 year after randomization (Figure 1A and B). The association between PVI and locoregional failure was not statistically significant for postmenopausal patients (trial IX; $P = 0.08$ and $P = 0.18$, respectively) but the patterns of recurrence were similar to those observed among premenopausal patients in trial VIII (Figure 1C and D).

PVI and DFS

Overall, DFS was significantly longer in patients whose tumors did not have PVI compared with those with PVI (Figure 2A and C). In univariate analyses, among premenopausal patients in trial VIII, the hazard of a DFS event was increased by 61% [HR 1.61, 95% confidence interval (CI) 1.2–2.1; $P < 0.001$] for patients with PVI present compared with patients without PVI. Among postmenopausal patients in trial IX, the hazard of a DFS event was increased by 27% in patients whose tumors had PVI (HR 1.27, 95% CI 1.04–1.5; $P = 0.02$) (Table 3).

Figure 2B and D summarizes DFS according to the tumor hormone receptor status and PVI. Among premenopausal patients (trial VIII), there was heterogeneity in the association of PVI with DFS according to the hormone receptor status ($P = 0.04$ for interaction; Table 3). The presence of PVI was associated with an increased hazard of a DFS event for patients with hormone receptor-present tumors (HR 1.83, 95% CI 1.38–2.43) that was not evident in patients with tumors that did not express hormone receptors (HR 1.08, 95% CI 0.63–1.84). DFS was longest for patients whose tumors expressed hormone receptors and were absent of PVI (Figure 2B); DFS for the remaining three subgroups was comparable by 7 years following randomization. Similarly, there was heterogeneity among postmenopausal patients (trial IX; $P = 0.02$ for interaction; Table 3). However, in contrast, the presence of PVI

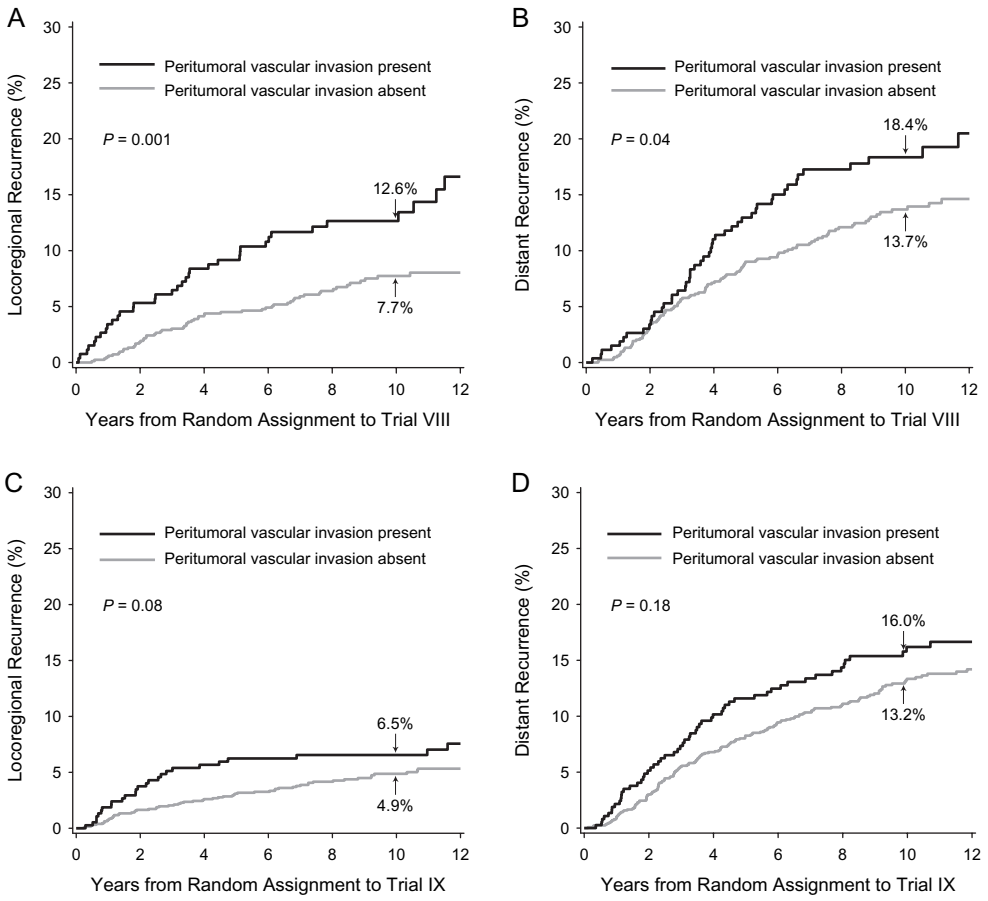

Figure 1. Cumulative incidence of (**A**) locoregional or (**B**) distant recurrence in trial VIII (premenopausal) according to the presence or absence of peritumoral vascular invasion and in trial IX [postmenopausal (**C** and **D**)].

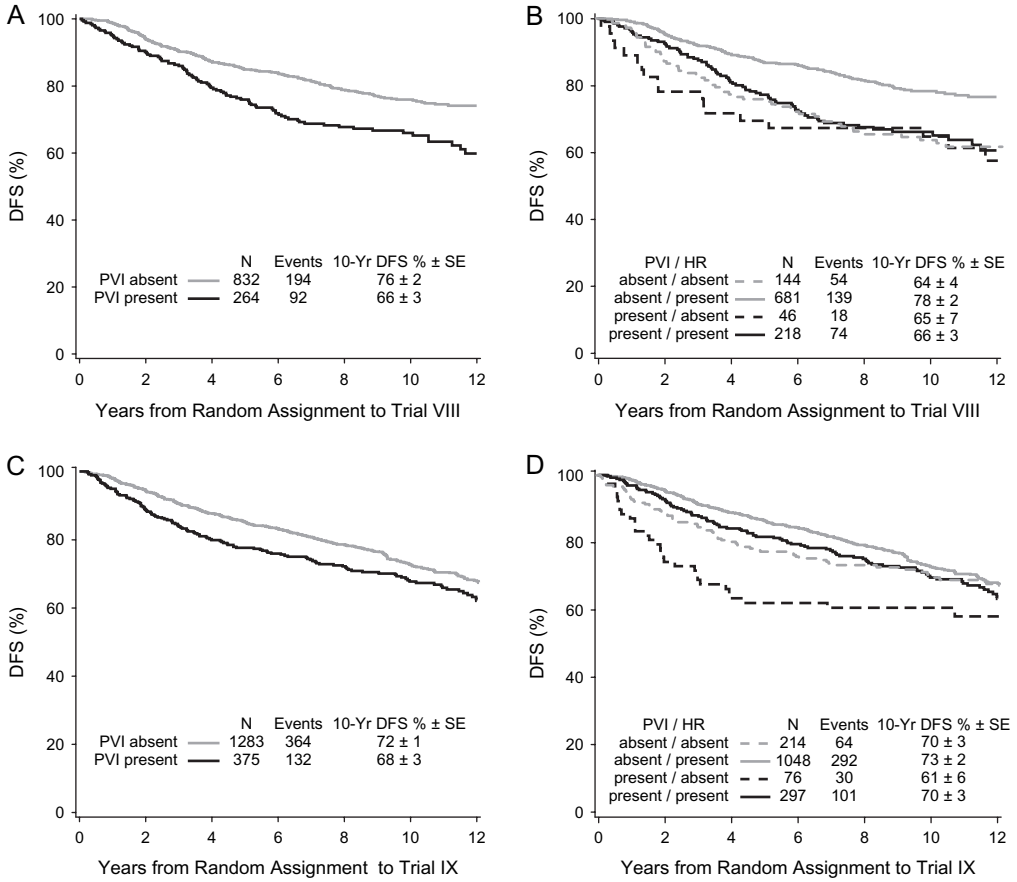

Figure 2. Disease-free survival (DFS) according to the presence or absence of peritumoral vascular invasion (PVI) for (**A**) trial VIII all premenopausal patients, (**B**) trial VIII according to hormone receptor status, (**C**) trial IX all postmenopausal patients and (**D**) trial IX according to hormone receptor status.

was associated with an increased hazard of a DFS event for patients with hormone receptor-absent tumors (HR 1.54, 95% CI 1.01–2.38) and not in patients with hormone receptor-present tumors (HR 1.19, 95% CI 0.95–1.49). For trial IX, the poorest DFS was observed in patients whose tumors were hormone receptor absent and PVI present (Figure 2D). When the models were adjusted for other covariates, the presence of PVI maintained its prognostic importance.

effects of treatments and PVI on DFS

In exploratory, hypothesis-generating analyses, we investigated the relative value of adjuvant treatments in patient cohorts defined by hormone receptor status.

hormone receptor-expressing tumors. Figure 3A and B summarizes DFS for premenopausal patients with hormone receptor-present tumors according to the PVI status and treatment in trial VIII. The plots indicate that with PVI present, treatments including goserelin provided more favorable DFS compared with CMF-only treatment or no treatment (Figure 3B). This observation was supported by the statistical models of adequate therapy, which showed a significant relationship between PVI and goserelin-containing treatment ($P = 0.03$ for interaction). When PVI was present, there was an increased hazard of a DFS event when treatment did not contain goserelin [HR (no goserelin : goserelin) = 1.75, 95% CI 1.11–2.76], but similar benefits of all treatments when tumors did not manifest PVI [HR (no goserelin : goserelin) = 0.94, 95% CI 0.66–1.32] (Table 4).

We further explored 'inadequate' therapy with CMF alone according to age, as the results of trial VIII indicated poorer outcome among younger premenopausal patients treated with CMF alone for hormone receptor-expressing tumors. There

Table 3. The association of presence of PVI with DFS, among all patients and for subgroups defined by hormone receptor status

	DFS hazard ratio (95% CI) for effect of PVI presence : absence	
	Trial VIII (premenopausal)	Trial IX (postmenopausal)
All patients	1.61 (1.20–2.10); $P = 0.0001$	1.27 (1.04–1.50); $P = 0.02$
Hormone receptor status[a]		
Present	1.83 (1.38–2.43)	1.19 (0.95–1.49)
Absent	1.08 (0.63–1.84)	1.54 (1.01–2.38)

[a]There was heterogeneity in the association of PVI with DFS according to hormone receptor status: trial VIII, $P = 0.04$ for interaction; trial IX, $P = 0.02$ for interaction.

PVI, peritumoral vascular invasion; DFS, disease-free survival; CI, confidence interval.

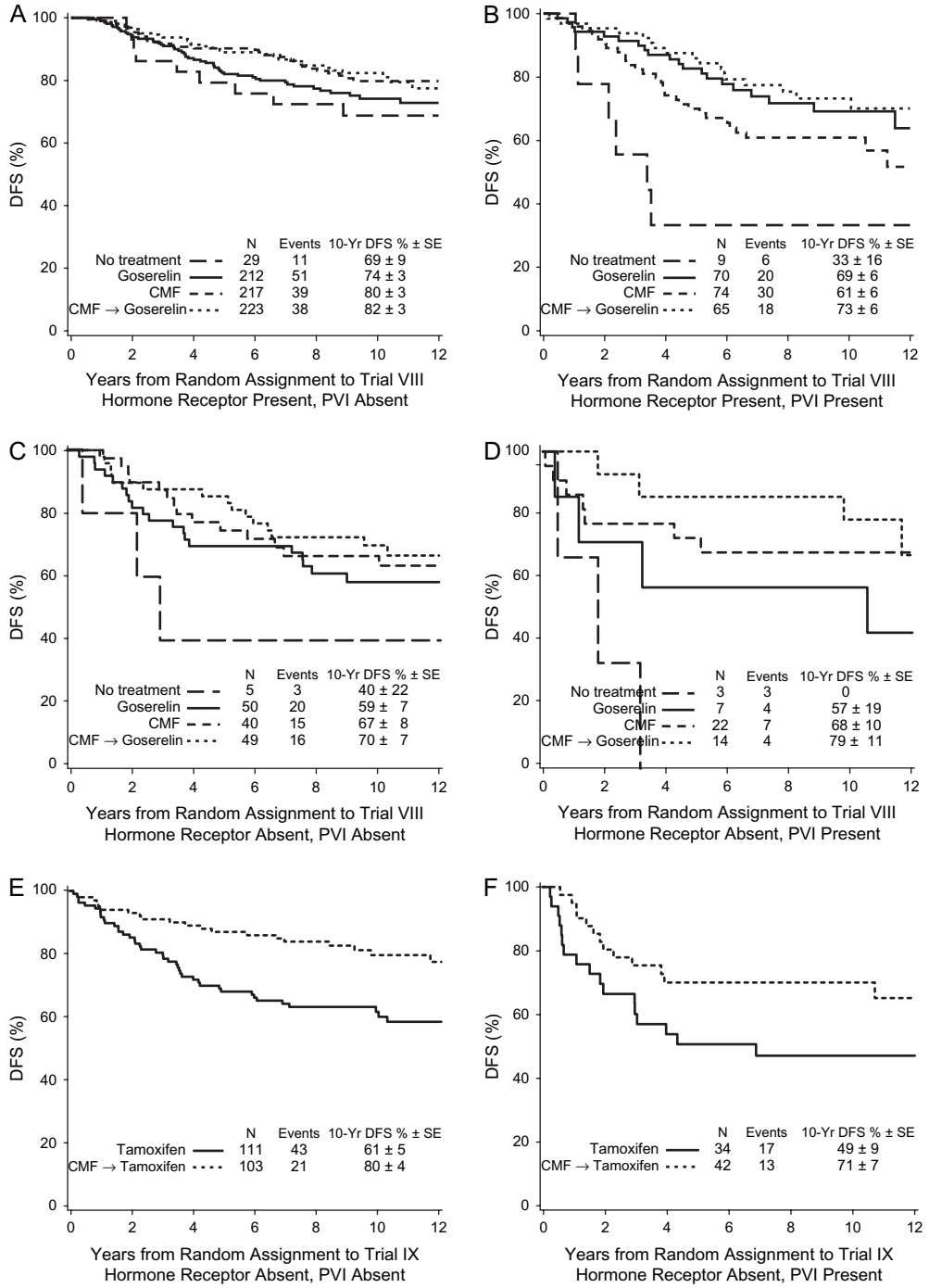

Figure 3. Disease-free survival (DFS) according to hormone receptor status, presence or absence of peritumoral vascular invasion (PVI) and treatment. (**A**) trial VIII (premenopausal), hormone receptor present, PVI absent; (**B**) trial VIII, hormone receptor present, PVI present; (**C**) trial VIII, hormone receptor absent, PVI absent; (**D**) trial VIII, hormone receptor absent, PVI present; (**E**) trial IX (postmenopausal), hormone receptor absent, PVI absent and (F) trial IX, hormone receptor absent, PVI present.

was a suggestion of a differential association of PVI with DFS according to age ($P = 0.05$ for interaction); DFS was adversely influenced by the presence of PVI with the effect upon younger premenopausal patients more pronounced (HR 6.65, 95% CI 2.80–15.70) than upon older premenopausal patients (HR 2.29, 95% CI 1.34–4.30).

In the original trial IX results, there was no benefit of CMF preceding tamoxifen versus tamoxifen alone among these postmenopausal women with ER-expressing tumors; this result was observed regardless of whether PVI was present or absent ($P = 0.67$ for interaction; Table 4).

Hormone receptor-absent tumors. Somewhat parallel, though less clear, results were seen in premenopausal patients with receptor-absent tumors and CMF-containing treatments (Figure 3C and D, $P = 0.11$ for interaction). Patients with

Table 4. The association of adequate adjuvant therapy and PVI with DFS according to tumor hormone receptor status

	DFS hazard ratio (95% CI)		Interaction
	PVI absent	PVI present	*P* value
Trial VIII (premenopausal)			
Hormone receptor present			
Inadequate (no goserelin) : adequate (goserelin)	0.94 (0.66–1.32)	1.75 (1.11–2.76)	0.03
Hormone receptor absent			
Inadequate (no CMF) : adequate (CMF)	1.32 (0.77–2.26)	3.20 (1.24–8.26)	0.11
Trial IX (postmenopausal)			
Hormone receptor present			
CMF → Tam : Tam	0.94 (0.75–1.19)	1.04 (0.70–1.54)	0.67
Hormone receptor absent			
Adequate (CMF → Tam) : adequate (Tam)	0.46 (0.27–0.77)	0.52 (0.25–1.06)	0.79

PVI, peritumoral vascular invasion; DFS, disease-free survival; CI, confidence interval; CMF, cyclophosphamide, methotrexate and 5-fluorouracil chemotherapy; Tam, tamoxifen.

receptor-absent tumors with PVI had a threefold increase in the hazard of a DFS event when treatment did not contain CMF [HR (no CMF : CMF) = 3.20, 95% CI 1.24–8.26], but more similar benefits of treatments when PVI was absent [HR (no CMF : CMF) = 1.32, 95% CI 0.77–2.26] (Table 4).

Among the postmenopausal patients in trial IX, the benefit of additional CMF preceding tamoxifen compared with tamoxifen alone was seen exclusively in patients whose tumors did not express ER. The benefit of chemotherapy was similar in cohorts with or without PVI (Table 4, Figure 3E and F), with the hazard of a DFS event approximately halved by treatment with CMF followed by tamoxifen versus tamoxifen alone.

discussion

Metastasis is the dominant lethal event in breast cancer. Since most metastasis must spread through lymphatic or blood vessels, it is intuitively likely that the demonstration of tumor invasion of vascular spaces should be an adverse prognostic indicator. Such an association has been reported in several series [1–9], though not others [24, 25]. Earlier work from the IBCSG has shown that the presence of vascular invasion predicts the presence of occult lymph node metastases on serial sectioning [14] and predicts the presence of positive sentinel nodes [15]. Thus, patients identified in these studies as node negative by routine pathological assessment, but whose tumors showed PVI, may in fact have harbored undetected nodal metastases. It should follow that the conclusions of this study may extend to patients with at least some detectable nodal involvement.

It has been claimed that factor VIII staining can help discriminate between blood and lymphatic vessel spaces [26–28], though others have questioned the reliability of this marker [29, 30]. More recently, the marker D2-40 has been used to distinguish lymphatic from blood vessel invasion [31, 32]. Our study was based on routine review of hematoxylin–eosin-stained slides by standard criteria [1], and no attempt was made to discriminate between blood vessel and lymphatic vessel invasion. Like Pinder et al. [6], we found that PVI was associated with tumor grade and tumor size (in trial IX postmenopausal patients only), but not with menopausal status or hormone receptor expression.

It might be expected that vascular invasion, especially lymphatic vessel invasion, could predict locoregional failure. Such an association has been reported [6] among patients who received no systemic adjuvant therapy. In our series, the association between PVI and locoregional failure was marked in trial VIII in which some premenopausal patients were treated without specific endocrine adjuvant therapy, but was marginal in trial IX, in which all postmenopausal patients received tamoxifen.

The prognostic significance of PVI for DFS was particularly evident among participants in the premenopausal trial VIII in which some patients were treated without endocrine adjuvant therapy despite the presence of hormone receptors. We have since described a poorer prognosis among younger patients with receptor-positive breast cancer treated only with chemotherapy [19].

We observed a particularly strong adverse prognostic effect of PVI among the small number of patients who were assigned no adjuvant therapy in the earlier part of trial VIII (Figure 3B), a finding reminiscent of the strong effect seen in the Nottingham series [6] in which no adjuvant systemic therapy was given. We also found an adverse prognostic effect in trial VIII among patients with receptor-positive tumors treated only with CMF chemotherapy, especially those aged ≤40 years, perhaps reflecting the unreliable ovarian-suppressive effects of CMF in younger premenopausal patients [16], while older patients treated with CMF alone may have derived partial endocrine therapeutic benefit from chemotherapy-induced ovarian suppression.

It was also striking that the adverse prognostic effect of omitting goserelin treatment of premenopausal patients (trial VIII) with receptor-positive disease was confined to patients whose tumors showed PVI (HR 1.75) and completely absent (HR 0.94) among those whose tumors did not. In contrast, the adverse effect of omitting CMF in hormone receptor-negative disease was less clearly linked to PVI. In postmenopausal patients with receptor-negative disease, the effect of omitting CMF was similar in the presence or absence of PVI.

The present study, although based on large prospective randomized trials, involves retrospective subset analyses and may reflect the play of chance. We therefore encourage clinical trial groups with series of patients with node-negative, endocrine-responsive disease to examine the impact of PVI. If confirmed, the abrogation of the adverse effect of PVI by endocrine therapy and the association between PVI and the efficacy of endocrine therapy might indicate that endocrine therapy has a specific role in the later stages of the metastatic process such as implantation and angiogenesis: a role apparently not shared by adjuvant cytotoxic therapy of overall similar efficacy. Conversely, it is possible that PVI is a marker for tumor cells particularly sensitive to endocrine therapy.

Our study indicates that, in premenopausal patients, the presence of PVI in receptor-positive tumors without lymph node metastases carries adverse prognostic significance, which can be overcome by appropriate specific endocrine adjuvant therapy.

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IBCSG: Participants and Authors:

Scientific Committee: A. Goldhirsch and A.S. Coates (Co-Chairs).

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Coordinating Center, Bern, Switzerland: M. Castiglione-Gertsch (Study Chair), A. Hiltbrunner (Director); G. Egli, M. Rabaglio, R. Maibach, R. Studer, B. Ruepp and E. Marbot; Pathology Office: R. Kammler (Head Pathology Coordinating Office), H.-R. Pauli, A. Aeschbacher and S. Oelhafen.

Statistical Center, Harvard School of Public Health and Dana-Farber Cancer Institute, Boston, MA, USA: R.D. Gelber (Group Statistician), K. Price (Director of Scientific Administration), A. Giobbie-Hurder, M. Regan, S. Gelber, Z. Sun, B. Cole and L. Nickerson.

Data Management Center, Frontier Science and Technology Research Foundation, Amherst, NY, USA: L. Blacher (Director), R. Hinkle (Trial Data Manager), S. Lippert and J. Celano.

Pathology Office, European Institute of Oncology, Milan, Italy: G. Viale, E. Maiorano, M. Mastropasqua, S. Andrighetto, G. Peruzzotti, R. Ghisini, E. Scarano, P. Dell'Orto and B. Del Curto.

Pathology Office, University of Glasgow, Scotland, UK: B. Gusterson and E. Mallon.

The Ontario Cancer Treatment and Research Foundation, Toronto Sunnybrook Regional Cancer Centre, Toronto, Canada: K. Pritchard, D. Sutherland, C. Sawka, G. Taylor, R. Choo, C. Catzavelos, K. Roche and H. Wedad.

National Institute of Oncology, Budapest, Hungary: I. Láng, E. Hitre, E. Juhos, I. Szamel, J. Toth, Z. Orosz and I. Peter.

Centro di Riferimento Oncologico, Aviano, Italy: D. Crivellari, S. Monfardini, E. Galligioni, M.D. Magri, A. Veronesi, A. Buonadonna. S. Massarut, C. Rossi, E. Candiani, A. Carbone, T. Perin, R. Volpe, M. Roncadin, M. Arcicasa, F. Coran and S. Morassut.

Spedali Civili and Fondazione Beretta, Brescia, Italy: E. Simoncini, G. Marini, P. Marpicati, M. Braga, P. Grigolato and L. Lucini.

General Hospital, Gorizia, Italy: S. Foladore, L. Foghin, G. Pamich, C. Bianchi, B. Marino, A. Murgia and V. Milan

European Institute of Oncology, Milano, Italy: A. Goldhirsch, M. Colleoni, G. Martinelli, L. Orlando, F. Nolé, A. Luini, R. Orecchia, G. Viale, G. Renne, G. Mazzarol, F. Peccatori, F. de Braud, A. Costa, S. Zurrida, P. Veronesi, V. Sacchini, V. Galimberti, M. Intra, S. Cinieri, G. Peruzzotti and U. Veronesi.

Ospedale Infermi, Rimini, Italy: A. Ravaioli, D. Tassinari, G. Oliverio, F. Barbanti, P. Rinaldi, L. Gianni and G. Drudi.

Ospedale S. Eugenio, Roma, Italy: M. Antimi, M. Minelli, V. Bellini, R. Porzio, E. Pernazza, G. Santeusanio and L.G. Spagnoli.

Ospedale S. Bortolo, Vicenza, Italy: M. Magazu, V. Fosser, P. Morandi, G. Scalco, M. Balli, E.S.G. d'Amore, S. Meli and G. Torsello.

The Institute of Oncology, Ljubljana, Slovenia: J. Lindtner, D. Erzen, E. Majdic, B. Stabuc, A. Plesnicar, R. Golouh, J. Lamovec, J. Jancar, I. Vrhovec and M. Kramberger.

Groote Schuur Hospital and University of Cape Town, Cape Town, Republic of South Africa: D.M. Dent, A. Gudgeon, E. Murray, G. Langman, I.D. Werner, P. Steynor, J. Toop and E. McEvoy.

Sandton Oncology Center, Johannesburg, Republic of South Africa: D. Vorobiof, M. Chasen, G. Fotheringham, G. de Muelenaere, B. Skudowitz, C. Mohammed, A. Rosengarten and C. Thatcher.

Madrid Breast Cancer Group, Madrid, Spain: H. Cortés-Funes, C. Mendiola, J. Hornedo, R. Colomer, F. Cruz Vigo, P. Miranda, A. Sierra, F. Martinez-Tello, A. Garzon, S. Alonso and A. Ferrero.

West Swedish Breast Cancer Study Group, Göteborg, Sweden: C.M. Rudenstam, M. Suurküla, Ö. Sjukhuset,G. Havel, S. Persson, J.H. Svensson, G. Östberg, S.B. Holmberg, A. Wallgren, S. Ottosson-Lönn, R. Hultborn, G. Colldahl-Jäderström, E. Cahlin, J. Mattsson, L. Ivarsson, O. Ruusvik, L.G. Niklasson, S. Dahlin, G. Karlsson, B. Lindberg, A. Sundbäck, S. Bergegårdh, H. Salander, C. Andersson,

M. Heideman, Y. Hessman, O. Nelzén, G. Claes, T. Ramhult, A. Kovacs and P. Liedberg.

Swiss Group for Clinical Cancer Research (SAKK) member institutions—Inselspital, Bern, Switzerland: M.F. Fey, M. Castiglione-Gertsch, E. Dreher, H. Schneider, S. Aebi, J. Ludin, G. Beck, A. Haenel, J.M. Lüthi, L. Mazzucchelli, J.P. Musy, H.J. Altermatt, M. Nandedkar and K. Buser.

Kantonsspital, St Gallen, Switzerland: H.J. Senn, B. Thürlimann, Ch. Oehlschlegel, G. Ries, M. Töpfer, U. Lorenz, O. Schiltknecht, B. Späti, A. Ehrsam, M. Bamert and W.F. Jungi.

Istituto Oncologico della Svizzera Italiana, Bellinzona, Switzerland: F. Cavalli, O. Pagani, H. Neuenschwander, L. Bronz, C. Sessa, M. Ghielmini, T. Rusca, P. Rey, J. Bernier, E. Pedrinis, T. Gyr, L. Leidi, G. Pastorelli, G. Caccia and A. Goldhirsch.

Kantonsspital, Basel, Switzerland: R. Herrmann, C.F. Rochlitz, J.F. Harder, S. Bartens, U. Eppenberger, J. Torhorst and H. Moch.

Hôpital des Cadolles, Neuchâtel, Switzerland: D. Piguet, P. Siegenthaler, V. Barrelet, R.P. Baumann and B. Christen.

University Hospital, Zürich, Switzerland: B. Pestalozzi, C. Sauter, D. Fink, M. Fehr, U. Haller, U. Metzger, P. Huguenin and R. Caduff.

Centre Hospitalier Universitaire Vandois, Lausanne, Switzerland: L. Perey, S. Leyvraz, P. Anani, F. Gomez, D. Wellman, G. Chapuis, P. De Grandi, P. Reymond, M. Gillet, J.F. Delaloye, C. Genton and M. Fiche.

Hôpital Cantonal, Geneva, Switzerland: P. Alberto, H. Bonnefoi, P. Schäfer, F. Krauer, M. Forni, M. Aapro, R. Egeli, R. Megevand, E. Jacot-des-Combes, A. Schindler, B. Borisch, S. Diebold, M. Genta and M. Pelte.

Kantonsspital Graubünden, Chur, Switzerland: F. Egli, P. Forrer, A. Willi, R. Steiner, J. Allemann, T. Rüedi, A. Leutenegger, U. Dalla Torre and H. Frick.

Australian New Zealand Breast Cancer Trials Group (ANZ BCTG) member institutions—Operations Office, University of Newcastle: J.F. Forbes and D. Lindsay.

The Cancer Council Victoria (previously Anti-Cancer Council of Victoria), Clinical Trials Office, Melbourne: J. Collins, R. Snyder, B. Brown, E. Abdi, H. Armstrong, A. Barling, R. Basser, P. Bhathal, W.I. Burns, M. Chipman, J. Chirgwin, I. Davis, R. Drummond, D. Finkelde, P. Francis, D. Gee, G. Goss, M. Green, P. Gregory, J. Griffiths, S. Hart, D. Hastrich, M. Henderson, R. Holmes, P. Jeal, D. Joseph, P. Kitchen, P. Kostos, G. Lindeman, B. Mann, R. McLennan, L. Mileshkin, P. Mitchell, C. Murphy, S. Neil, I. Olver, M. Pitcher, A. Read, D. Reading, R. Reed, G. Richardson, A. Rodger, I. Russell, M. Schwarz, S. Slade, R. Stanley, M. Steele, J. Stewart, C. Underhill, J. Zalcberg, A. Zimet, C. Dow and R. Valentine.

Flinders Medical Centre, Bedford Park, South Australia: T. Malden.

Mount Hospital, Perth, Western Australia: G. Van Hazel.

Calvary Mater Newcastle, Newcastle, Australia: J.F. Forbes, S. Braye, J. Stewart, D. Jackson, R. Gourlay, J. Bishop, S. Cox, S. Ackland, A. Bonaventura, C. Hamilton, J. Denham, P. O'Brien, M. Back, S. Brae and R. Muragasu.

Prince of Wales, Randwick, New South Wales, Australia: M. Friedlander, B. Brigham and C. Lewis.

Royal Adelaide Hospital, Adelaide, Australia: I.N. Olver, D. Keefe, M. Brown, P.G. Gill, A. Taylor, E. Yeoh, E. Abdi, J. Cleary and F. Parnis.

Sir Charles Gairdner Hospital, Nedlands, Western Australia: M. Byrne, G. Van Hazel, J. Dewar, M. Buck, G. Sterrett, D. Ingram, D. Hastrich, D. Joseph, F. Cameron, K.B. Shilkin, P. Michell, J. Sharpio, G. Harloe, J. Lewis, B. Snowball, P. Garcia Webb, J. Harvey, W.D. De Boer, P. Robbins, N. Buxton and M.N.I Walters.

University of Sydney, Dubbo Base Hospital and Royal Prince Alfred Hospital, Sydney, Australia: J. Beith, M.H.N. Tattersall, A.S. Coates, F. Niesche, R. West, S. Renwick, J. Donovan, P. Duval, R. J. Simes, A. Ng, D. Glenn, R.A. North, R.G. O'Connor, M. Rice, G. Stevens, J. Grassby, S. Pendlebury, C. McLeod, M. Boyer, A. Sullivan, J. Hobbs, D. Lind, J. Grace and P. McKenzie.

W.P. Holman Clinic, Launceston, Australia: D. Boadle, T. Brain, I. Byard and D. Byram.

Auckland Breast Cancer Study Group, Auckland, New Zealand: V.J. Harvey, R.G. Kay, P. Thompson, D. Porter, C.S. Benjamin, A. Bierre, M. Miller, B. Hochstein, A. Lethaby, J. Webber, J.P. Allen, M. Allon, J.F. Arthur, M. Gurley, P. Symmans, M. Christie and A.R. King.

Waikato Hospital, Hamilton, New Zealand: I. Kennedy, G. Round and J. Long

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