Patients: All 6671 patients (2594 node-negative; 4077 node-positive) from IBCSG trials I-IX fulfilling predefined criteria were included. The treatment consisted of modified radical mastectomy without PRT and adjuvant systemic therapy (i.e., at least three courses of CMF chemotherapy or tamoxifen). Central pathology review had been performed for most patients. Multiple regression modeling of the cumulative LRR incidence was used to identify significant predictors of risk.

Results: At a median follow-up of 9–22 years, LRR (with or without distant failure) was found in 1253 patients. The median number of nodes examined was 14. In the node-negative cohort, vessel invasion increased the risk, and number of nodes examined (postmenopausal) decreased the risk of LRR, but no risk group reached 20% 10-year LRR incidence. In the node-positive cohort, number of positive nodes, tumor grade, vessel invasion (premenopausal) and number of uninvolved nodes were significant predictors. Among patients with 1–3 positive nodes a high tumor grade, vessel invasion and few uninvolved nodes defined a high risk for LRR.

Conclusion: A low number of examined nodes in some trials may explain the reported success of PRT in patients with 1–3 involved nodes. When the median number of nodes examined is higher, tumor grade and vessel invasion may define subgroups of patients with breast cancer and 1–3 involved axillary lymph nodes with such a high risk for LRR that PRT may be indicated.

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ONCOPOOL – A European dataset in 16,893 cases of breast cancer

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The SEER data (Henson 1991, Carter 1989) has long been regarded as providing the best information on the characteristics of breast cancers at diagnosis and on outcomes.

Survival has improved greatly since the 1980's across the prognostic range. ONCOPOOL (FP 5 EC Grant) is a dataset from 11 European units, with QA and long term follow up.

Consecutive cases (n = 16,693) in years between 1990 and 1999 were entered. This has given up to date information on treatments and of Pathology and biological factors at diagnosis and the effect of these on recurrence and survival (Tables 1 and 2)

Table 1. Percentages on Pathology

Tumour size (cm)	0–1	1.01–2	20.1–3	3.01–4	4.01–5
%	26	49	19	5	2
Lymph node status	Negative		Positive <4		Positive >4
%	66		24		10
Grade	I		II		III
%	29		42		29

Table 2. Survival according to Nottingham Prognostic Index (NPI)

NPI Group	% in group	% 10 year survival (actuarial)
Excellent	20	95.6
Good	27	91.4
Moderate I	26	81.7
Moderate II	16	72.7
Poor	11	50.8

A great deal more data on presentation, primary and local and systemic adjuvant therapies, pathological and biological make-up, recurrence and survival outcomes are being analysed, ONCOPOOL should now be regarded as the key dataset.

References

[1] Relationship among outcome, stage of disease and histologic grade for 22,616 cases of breast cancer. Cancer: (1991) November 15, Vol.68, 2142–2149.

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A rare cancer network multicenter study on phyllodes tumor and sarcomas of the breast

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Objective: Phyllodes tumor (PT) of the breast and primary breast sarcomas (PBS) are rare neoplasms. Their management has been mainly based on surgery. The role of adjuvant treatments such as radiation or chemotherapy (RT) remains unclear. The aim of this study was to evaluate the outcome and identify prognostic factors for local control and survival.

Materials and Methods: Data from 443 women with PT of the breast and 103 breast sarcomas were analyzed. For PT patients, the median age was 40 years (12–87) with a median histologic tumor size of 3 cm (0.5–30 cm). Tumors were classified as benign in 284 (64%), borderline in 80 (18%), and malignant in 79 (18%) cases. Surgery consisted of wide excision in 377 (85%) and mastectomy in 66 (15%) cases. Thirty-nine (9%) patients received adjuvant RT (50 Gy in 25 fractions).

In the PBS patients, median age was 55 years (13–86). Median histologic tumor size was 4.45 cm (0.8–22 cm). There were 42 angiosarcomas. Therapeutic strategy consisted of neo-adjuvant chemotherapy followed by loco-regional treatment in 19 patients, surgery alone in 38, and conservative surgery followed by RT in 30 patients. RT as initial treatment was delivered in 50 patients (50 Gy in 25 fractions).

Results: The median follow-up was 106 and 64 months respectively for PT and PBS patients. Multivariate analysis in **PT** showed six favorable independent prognostic factors for local control: benign histology, no cellular atypia, no residual tumor ((NRT) after initial treatment, total mastectomy, negative margins, and association of RT. For DFS, the four favorable independent factors were benign histology, low number of mitosis, NRT after initial treatment, and no personal history of breast disease.

For PBS, multivariate analysis revealed three favorable independent prognostic factors for local control: NRT after initial treatment, no cellular pleomorphism, and histology other than angiosarcoma. For the DFS, the five favorable independent factors were no menopausal status, NRT after initial treatment, histology other than angiosarcoma, absence of tumor necrosis, and histological grade 1–2.

Conclusions: In this large retrospective study of PT and PBS of the breast, the histological criteria of the tumor and the absence of residual tumor after first treatment are the main prognostic factors for outcome. In PT, while benign tumors have a good prognosis after surgery alone, adjuvant RT should be discussed in the management of malignant and borderline forms. We also confirmed the severe prognosis of angiosarcoma.

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Using changes in gene expression as assessed by microarray analysis of sequential tumour biopsies to predict response to neoadjuvant therapy with letrozole

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Selection of patients for endocrine therapy requires the identification of markers which accurately predict response or resistance. The advent of microarray analysis offers the opportunity to identify novel indices of responsiveness.

In the present study changes in gene expression profiles occurring within 10–14 days have been related to clinical response at 3 months in patients treated neoadjuvantly with letrozole. 58 postmenopausal women with large primary ER-rich breast cancers were treated with letrozole (2.5 mg/daily) for 3 months. Tumour biopsies were taken before and after 10–14 days treatment and RNA from the biopsies used to generate cRNA for hybridization on Affymetrix U-133A chips.

Comparison of gene profiles in paired biopsies confirmed that classical markers of oestrogen action (Trefoil factors 1 and 3, LIV-1, KIAA0101) and proliferation (Cyclin D1, Cyclin B2, CKS2, cell division cycle 2) change with treatment. Clinical response was determined from serial ultrasound measurements and was assessable in 52 cases; 37 (71%) responded (>50% reduction in tumour volume) and 15 were classified

as minimal response (<50% reduction in tumour volume). Changes in expression of 125 gene probes were informative in predicting for clinical response and when clustered, distinguished between responding and non-responding tumours with the exception of a single case. Whilst the ontology of the informative genes included protein metabolism (26%), transcription/translation (18%), signal transduction (14%), cell proliferation/apoptosis (14%), changes in none of the classical markers of oestrogen action and proliferation were predictive of response.

It is concluded that changes in pattern of gene expression can be detected as early as 14 days into treatment with neoadjuvant letrozole. A subset of genes allows for discrimination between tumours subsequently responding to letrozole and those that do not but these do not include classical markers.

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Young age is not an independent prognostic factor

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A common contention is that breast cancers in young women have worse prognoses than similar tumours in older women. In a publication (Kollias) we showed that poorer overall survival was due to the higher proportion of grade III tumours. Once standard prognostic factors had been taken into account (by use of the Nottingham prognostic Index – NPI) survival was no different from that in older women.

Survival has improved in all NPI groups in the last 15 years and the contention remains that young age is an adverse prognostic factor. A new study in tumours diagnosed 1990–99 is reported. 185 consecutive cases in women aged <40 compared with 477 cases aged 40–49 and 687 cases aged 50–59. Overall 10 year % survivals were 73, 80, 82 respectively.

Table 1. Distribution of grade and NPI at presentation (%)

Age	Grade			NPI Group				
	1	2	3	EPG	GPG	MPGI	MPGII	PPG
<40	8	24	69	5	13	24	33	25
40–49	17	30	53	11	17	30	27	14
50–59	24	38	38	19	24	27	17	13

Table 2. Survival by NPI (10 year actuarial %)

Group	Age		
	<40	40–49	50–59
EPG	100	100	96
GPG	84	96	97
MPGI	78	78	84
MPGII	81	76	64
PPG	49	54	50

Conclusions:

1. Overall survival is worse in women <40.
2. Poorer overall survival is due to more grade III cases and less grade I cases in young women, placing more into the Poor Prognostic Group.
3. Survival depends on the prognostic factors of the tumour at all ages and young age is not an independent prognostic factor.
4. The difference between this report and other series may be due to the prescription of adjuvant systemic therapies: in ER positive women regardless of age at Nottingham City Hospital hormonal adjuvant therapy is the treatment of choice whereas in many centres cytotoxic therapy is used for young women.

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Which cyclin E prevails as prognostic marker for breast cancer? Results from a retrospective study involving 635 lymph node negative breast cancer patients

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Purpose: To evaluate the prognostic value of cyclin E with a quantitative method for lymph node negative (LNN) primary breast cancer patients.

Patients and Methods: mRNA transcripts of full length and splice variants of cyclin E1 (*CCNE1*) and cyclin E2 (*CCNE2*) were measured by real time PCR in frozen tumor samples from 635 LNN breast cancer patients who had not received neoadjuvant or adjuvant systemic therapy.

Results: None of the PCR assays designed for the specific splice variants of the cyclins gave additional prognosis-related information compared with the common assays able to detect all variants. In Cox multivariate analysis, corrected for the traditional prognostic factors, high levels of cyclin E were independently associated with a short distant metastasis-free survival [hazard ratio (HR) = 3.40, P < 0.001 for *CCNE1*, and HR = 1.76, *P*<0.001 for *CCNE2*, respectively]. After dichotomizing the tumors at the median level of 70% tumor cells, the multivariate analysis showed particularly strong results for *CCNE1* in the group of 433 patients with primary tumors containing 30% or more stromal components (HR = 5.12, *P*<0.001). In these tumors, the worst prognosis was found for patients with estrogen-receptor negative tumors expressing high *CCNE1* (HR = 9.89, *P*<0.001) and for patients with small (T1) tumors expressing high *CCNE1* (HR = 8.47, *P*<0.001).

Conclusion: Our study shows that both *CCNE1* and *CCNE2* qualify as independent prognostic markers for LNN breast cancer patients, and that especially *CCNE1* may provide additional information for specific subgroups of patients.

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Prognosis of operable breast cancer in young patients treated in a single Institution: independent pejorative value of positive Estrogen Receptor

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Purpose: According to consensus conferences for adjuvant treatments in breast cancer, young age is considered as a main criteria to justify chemotherapy. However, no multivariate prognostic analysis including clinical or biological factors has yet been published for this population.

In order to identify a good prognostic subgroup of young patients who don't require adjuvant chemotherapy, we selected in the Institut Bergonié Breast Unit database 255 patients younger than 40 whose tumors were primarily resected between 01/01/85 and 12/31/01 for a breast adenocarcinoma (group A). Characteristics of this population were compared to a group of 979 older patients (40–49) operated on at the same time (group B). A prognostic factors analysis was performed in group A.

Results: No significant differences were observed between the two groups for pT, rate of pN+, of ER+ and PR+. However, modified SBR grade, peritumoral emboli, mitotic count and lymphoid infiltration were significantly higher in group A. Rates of lumpectomy and adjuvant radiotherapy were similar in the two groups. Group A patients received chemotherapy more frequently (62% versus 47%) (p = 4x10–5). Considering ER+ tumors, hormonal treatment was more frequently prescribed in group B (5% vs 16% p = 2x10–4).

With a 10 year median follow-up, we confirmed a worse prognosis in younger patients: 10 years overall survival (66% vs 82% – $p = 3\times10^{-7}$), 10 years local relapse free probability (73% vs 85% – $p = 3\times10^{-4}$) and metastatic relapse free probability (60% vs 78% – $p = 2\times10^{-9}$).

Prognostic analysis of metastatic relapse in group A showed that pT2–3, pN1, peritumoral emboli, mitotic count >15 and ER+ were significantly associated with a higher metastatic relapse rate in univariate analysis. Prognostic was not significantly different between $\leqslant$ 35 and 36–39 years old patients.

Three factors remained significantly predictive of distant relapse in multivariate analysis for group A: peritumoral emboli (OR = 2.61), ER+ (OR = 2.00), and mitotic count > 15 (OR = 1.85). Ten years metastatic relapse free rate was 90%, 75%, 43% and 40% for subgroups having 0, 1, 2 and 3 of these factors; only 6% of the patients had none of these three pejorative factors.

Conclusion: This retrospective study confirms worse prognosis for patients younger than 40. Unlike older patients, ER positivity is associated with a worse outcome. Patients with good prognosis enough to avoid chemotherapy are uncommon before 40.