

International Expert Panel on the Use of Primary (Preoperative) Systemic Treatment of Operable Breast Cancer: Review and Recommendations

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Abstract: Primary systemic therapy (PST) represents the standard of care in patients with locally advanced breast cancer. In addition, there is increasing information on PST in operable breast disease that supports the use of PST in routine practice. However, current regimens and techniques vary. To address this concern, a group of representatives from breast cancer clinical research groups in France, Germany, Italy, the United Kingdom, and the United States

reviewed all available data on prospective randomized trials in this setting. Recommendations are made regarding terminology, indications, regimen, diagnosis before treatment, monitoring of efficacy, tumor localization, surgery, pathologic evaluation, and postoperative treatment.

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REVISED GUIDELINES for the treatment of breast cancer outside clinical trials have been published by the National Institutes of Health in the United States and by the St Gallen Consensus Panel (St. Gallen, Switzerland) on the Treatment of Primary Breast Cancer.^{1,2} These recommendations, however, apply to patients with early stages of breast cancer. Approximately 10% to 30% of all primary breast cancers are diagnosed as locally advanced (eg, inflammatory cancer or cancer with skin, chest wall, or extensive regional lymph node involvement) or are carcinomas with an unfavorable breast-to-tumor size ratio. A large portion of these patient cases are excluded from prospective randomized systemic therapy trials and therefore are not included in the meta-analyses

conducted periodically by the Early Breast Cancer Trialists' Collaborative Group,³⁻⁵ on which many clinicians base their recommendations for the treatment of patients with breast cancer. These patients require different treatment strategies, and more appropriately, should receive systemic therapy before surgery.

In addition to the fact that the existing recommendations do not take all breast cancers into account, indications for primary systemic therapy (PST) have changed over time. Although patients with inoperable, locally advanced breast cancer represent the majority of those treated with PST in routine practice, there is an increasing tendency also to treat operable breast cancer with PST. However, the type of systemic treatment as well as the methods used for diagnosis, monitoring, and surgery currently vary.

Because several large randomized trials in operable disease now provide a much larger pool of evidence-based data than exists for locally advanced disease, it seems reasonable to summarize the available experience and to formulate recommendations for the use of PST in operable and (in part) for locally advanced disease.

BRIEF HISTORY OF THE USE OF PST

On the basis of the hypothesis of primary systemic disease and experiences in various animal models,⁶⁻¹⁰ PST was first introduced into clinical practice in the 1970s (Table 1). Tumor cells assumed to have disseminated before the diagnosis and independent of mechanical manipulations of the tumor by the surgeon were considered to be more sensitive to PST than to adjuvant systemic therapy (AST). High tumor regression rates of approximately 70% established PST as a standard treatment option for patients with inoperable locally advanced or inflammatory breast cancer.¹¹ In the late 1980s, the use of PST was shown to improve the breast-conserving surgery rate in up to 98% of patients with large operable breast tumors.¹²⁻¹⁹ During the same period, Forrest et al²⁰ demonstrated that PST allows the primary

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Table 1. Historic Development of Primary and Adjuvant Systemic Therapy in Breast Cancer

Decade	Indications for Primary Systemic Therapy in Breast Cancer	Indications for Adjuvant Systemic Therapy in Breast Cancer
1970s	Nonoperable (locally advanced or inflammatory) breast tumors	Node-positive
1980s	Operable large breast tumors (T > 5 cm)	Node-negative, receptor-negative (estrogen and/or progesterone)
1990s	Operable small breast tumors (T > 1-2 cm)	Node-negative, receptor-positive (estrogen and/or progesterone)
	Aims of Primary Systemic Therapy	Aims of Adjuvant Systemic Therapy
1970	—	Immediately after surgery, to destroy disseminated tumor cells induced by mechanical manipulation
1970s	To achieve operability in locally advanced tumors	To destroy micrometastases already present before surgery (for weeks or months)
1980s	To improve the breast conservation rate in operable breast cancer	To overcome drug resistance using new compounds (anthracyclines)
1990s	To destroy or alter multicentric or multifocal tumor cells in the breast (resulting in fewer ipsilateral in-breast recurrences)	To overcome drug resistance by increasing dose-intensity
> 2000	To select chemoresistant or sensitive tumors	To improve single-drug intensity by sequential application

tumor response to serve as an *in vivo*²¹ chemosensitivity test: A reduction in the primary tumor volume can be used to predict a reduction in micrometastatic tumor volume as well as clinical benefit.

Much of the evidence comparing PST with AST is from randomized controlled clinical trials in patients with operable (stage T1c-3, N0, M0 or T1-3, N1, M0) breast cancer. These studies have shown that primary (preoperative) systemic therapy

with cyclophosphamide, methotrexate, and fluorouracil²²; doxorubicin and cyclophosphamide (AC)²³; fluorouracil, doxorubicin, and cyclophosphamide²⁴; or fluorouracil, epirubicin, and cyclophosphamide²⁵ offers the same disease-free survival and overall survival benefits as does AST with the same drug combinations (Table 2). In addition, PST results in an increase in the proportion of patients who are subsequently shown to have axillary lymph nodes free of metastatic involvement or who become candidates for breast-conserving surgery.

Several clinical trials in operable breast cancer have compared different PST regimens in patients with breast tumor sizes as small as 1 to 2 cm (Table 3). Complete pathologic remission (pCR) of these tumors correlates strongly with both prolonged disease-free survival and overall survival²⁶⁻²⁹ (even though tumor progression during PST is rare [approximately 3%], its occurrence predicts a poor prognosis).^{14,25,26} The absence of identifiable tumor cells in the removed breast tissue has been reported in 6% to 19% of patients who have received PST (Table 3).³⁰⁻³⁶ In most of the large clinical trials that compare PST with AST, the primary chemotherapy regimens that result in higher pCR rates are also associated with a higher rate of successful breast conservation and a higher proportion of patients subsequently found to have axillary lymph nodes free of metastatic involvement. None of the larger trials has detected a disease-free survival or overall survival advantage in favor of PST. One small clinical trial showed a potential advantage with the use of preoperative chemotherapy because clinical response to the first regimen was used as a guide in selecting additional therapy.²⁹ At present, this approach has not been confirmed in a more appropriate trials setting and was not compared with conventional postoperative chemotherapy.

METHODS

In October 2001, representatives of a number of breast cancer clinical research groups from France, Germany, Italy, the United Kingdom, and the United States (see Appendix) were invited to join the panel. All representatives have been chairpersons of

Table 2. Overview of Randomized Trials Comparing Primary Systemic Therapy and Adjuvant Systemic Therapy in the Breast

Author and Group	No. of Patients	Tumor-Node-Metastasis Classification	Tumor Size (cm)	Regimen	Follow-up (months)	Local Failure Rate	Distant Failure Rate	Survival Rate	Breast Conservation (PST versus AST)
Fisher, ^{23,28} NSABP	1,523	T1-3, N0-1, M0	All	AC × 4	96	*	*	*	67% versus 60% P = 0.002
Gianni, ³⁵ ECTO	892	T1-3, N0-1, M0	≥ 2	AT-CMF	23	NA	NA	NA	71% versus 35% P < 0.0001
Van der Hage, ²⁵ EORTC	698	T1c-4d, N0-1, M0	≥ 1	FEC × 4	56	*	*	*	37% versus 21.% NA
Jakesz, ²² ABCSG	423	T1-3, N0-2, M0	All	CMF × 3†	NA	‡	*	*	*NA
Scholl, ²⁴ S6	390	T2-3, N0-2, M0	3-7	FAC × 4	66	*	*	*	82% versus 77%

Abbreviations: PST, primary systemic therapy; AST, adjuvant systemic therapy; NSABP, National Surgical Adjuvant Breast and Bowel Project; ECTO, European Cooperative Trial on Operable Breast Cancer; EORTC, European Organization for Research and Treatment of Cancer; ABCSG, Austrian Breast Cancer Study Group; S6, Study 6; NA, not available; AC, doxorubicin and cyclophosphamide; AT, doxorubicin and paclitaxel; CMF, cyclophosphamide, methotrexate, and fluorouracil; FEC, fluorouracil, epirubicin, and cyclophosphamide; EC, epirubicin and cyclophosphamide; FAC, fluorouracil, doxorubicin, and cyclophosphamide.

*No statistical difference between study arms.

†An additional three cycles of CMF or EC given postoperatively.

‡Statistically significant increase.

Table 3. Overview of Randomized Trials Comparing Different Primary Systemic Therapy Regimens in Breast Cancer

Author and Group	No. of patients	Tumor-Node-Metastasis Classification	Tumor Size (cm)	Regimen	Clinical Complete Response (%)	Pathologic Response* (%)	Breast Conservation Rate (%)
NSABP ³³	2,411	T1-3, N0-1, M0	All	AC × 4	40	9.8	61
				AC × 4, Doc × 4	65	18.7	63
Von Minckwitz, ³⁴ GABG	913	T2-3, N0-2, M0	≥ 2	AT × 4 q2w	32.5	7.7	65
				AC × 4, Doc × 4	57.4	16.1	75
Untch, AGO ³⁶	475†	T2-4d, N0-2, M0	≥ 3	ET × 4	NA	10	55
				Epi × 3, Tax × 3 q2w		18	66
Von Minckwitz, ³⁰ GABG	248	T2-3, N0-2	≥ 3	AT × 4 q2w	5.7	10.3	69
				AT × 4 q2w + Tam	12.5	9.1	69
Penault-Llorca, ³² France	200‡	NA	NA	AC	NA	6	45
				AT		15	56
Buzdar, ³¹ Houston	174	T1-3, N0-1, M0	≥ 1	FAC × 4	24	18	35
				Tax × 4	27	6	46
Smith, ²⁹ Scottish	104	T2-4, N0-2, M0	≥ 3	CVAP × 8	33	15.4§	48
				CVAP × 4, Tax × 4	56	30.8§	67

Abbreviations: NSABP, National Surgical Adjuvant Breast and Bowel Project; GABG, German Adjuvant Breast Cancer Group; AGO, Arbeitsgemeinschaft Gynäkologische Onkologie; AC, doxorubicin and cyclophosphamide; AT, doxorubicin and paclitaxel; ET, epirubicin and paclitaxel; Tam, tamoxifen; NA, not available; q2w, repeated every 2 weeks; CVAP, cyclophosphamide, vincristine, doxorubicin, prednisone; Doc, docetaxel; Epi, Epirubicin; Tax, paclitaxel.

*No invasive or in situ tumor cells in the removed breast.

†Interim analysis.

‡1:2 randomization.

§Including in situ residuals.

trials exploring PST or members of the corresponding trials' steering committees, or are reference experts for pathology, radiodiagnostics, or radiotherapy. Available data from all prospective randomized clinical trials on PST in operable breast cancer including at least 100 patients were critically reviewed with a goal of formulating a set of recommendations for the use of PST in operable breast cancer, both inside and outside clinical trials. Through a series of questions about terminology, indications, diagnosis, regimen, surgery, and radiotherapy, specialists representing biologic, pathologic, radiodiagnostic, surgical, and radiotherapeutic points of view arrived at a consensus and prepared the recommendations that follow. During the review process of the article, new trial results presented at the San Antonio Breast Cancer Conference in December 2001 and at the Annual Meeting of the American Society of Clinical Oncology at Orlando in May 2002 were included. Because the available amount of evidence-based data in the literature is limited, some answers contain review components that express educated opinions of the authors.

RECOMMENDATIONS FOR THE USE OF PST

The following sections describe the recommendations of the panel.

Recommended Terminology

PST refers to either the first postdiagnosis systemic treatment that a patient receives or indicates that additional subsequent therapy is intended. The term PST does not connote primacy in importance relative to other available interventions. In clinical practice, the terms downstaging,

induction therapy, and preoperative systemic therapy are often used in lieu of the preferred term PST when PST is administered to patients with small operable primary tumors to explore the sensitivity of the tumor to that therapy before surgery. The expression neoadjuvant therapy is also occasionally used, but this term is burdened with the connotation that it is of secondary importance to either surgical resection or radiation therapy, and we suggest that it be abandoned. We believe the term PST to be appropriate because it takes into account the order of administration, intended subsequent treatment, and efficacy of the systemic intervention

For Whom Is PST the Standard of Care?

Existing treatment patterns, although they are not based on the results of large randomized clinical trials, indicate that PST is considered the standard treatment for patients with inoperable primary breast cancer (ie, patients with locally advanced tumors for whom it is expected that local control cannot be attained by surgical means alone). In most cases, these patients represent a group with an unfavorable prognosis (stage IIIA-B or T3-4 disease), including classic inflammatory breast cancer or involvement of ipsilateral supra- or infraclavicular lymph nodes (N3). In operable breast cancer, PST can be considered as an alternative to AST.

For Whom Can PST Be Recommended as an Alternative to AST?

All large randomized clinical trials of PST versus AST indicate that these therapies offer patients equivalent disease-free survival and overall survival benefits (Table 2). PST is thus a reasonable alternative for patients with operable breast cancer

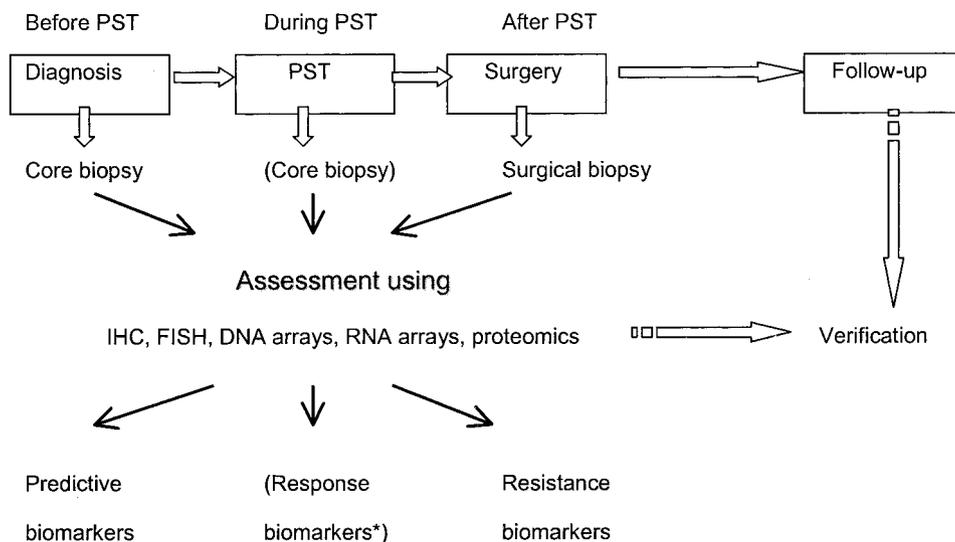


Fig 1. Assessment of markers for prediction, response, and resistance in the primary systemic therapy (PST) setting. IHC, immunohistochemistry; FISH, fluorescence in situ hybridization. *For research purposes only.

who are deemed to be appropriate candidates for mastectomy but who desire less extensive surgery (eg, breast-conservation surgery). PST is also increasingly used in patients who can technically have a lumpectomy first but whose physical appearance will be less damaged if PST is given first.

Numerous investigators have found that the rate of successful breast-conservation surgery is statistically significantly increased, as well as clinically relevant, in patients who receive PST compared with those who receive AST. Reported absolute differences in the rate of successful breast-conservation surgery between patients who receive PST and those who receive AST range from 5% to 36% (Table 2). The difference in the rate of successful breast-conservation surgery among patients who receive various primary systemic chemotherapy regimens ranges from 2% to 19% (Table 3).

In addition to the type of primary systemic chemotherapy, the rate of successful breast-conservation surgery also correlates with clinical response and the size of the primary tumor. Patients who experience a clinical complete response may have a successful breast-conservation rate of 90% and more.^{30,34} Patients who receive PST can increase their chance for breast conservation by 12.5% if the tumor size is 2 to 5 cm, and by 17.5% if the tumor size is more than 5 cm.²³ In the largest trial reported to date, in which patients had a median follow-up time of 8 years, no statistically significant difference was found in local recurrence-free survival between patients treated with PST (four cycles of AC) and those treated with AST (four cycles of AC).³⁷

The local recurrence rate among those who achieved complete clinical response was as low as 5.6%, and among those who did not achieve complete clinical response, the local recurrence rate was 9.7%. The local recurrence rate did not correlate with size of the primary tumor before treatment. However, among a small cohort of 69 patients who were considered candidates for mastectomy before receiving PST, a local recurrence rate of 14.5% was reported. This is in contrast to the 6.9% local failure rate seen among patients initially thought to be candidates for

breast-conservation surgery who received PST.²⁸ In another small trial,²² patients who did not respond to PST had a significantly increased risk of recurrence compared with those who did respond to PST.

These results are consistent with the hypothesis that a poor response to PST is a predictor of poor prognosis and a high risk of recurrence, irrespective of the type of surgery performed. The results may also indicate that patients who convert to breast-conserving surgery as a result of PST also have a higher risk of experiencing local treatment failure.

Because at present there is no evidence that PST offers a disease-free survival or overall survival benefit over AST, knowledgeable patients may choose to receive systemic therapy before surgical resection to take advantage of the response-assessment of the primary tumor before it is removed. A demonstrable response to PST may have a positive effect on the patient's compliance with additional treatment and on the patient's willingness to accept some adverse events. When the primary tumor increases in size during PST, immediate surgical intervention should be considered, with the aim of avoiding additional adverse effects of ineffective systemic treatment.

PST may also be advisable for certain patients who have medical contraindications to surgery or simply wish to delay surgery. For example, PST can be used in the second or third trimester in pregnant patients diagnosed with breast cancer; this is followed by surgery and radiotherapy after delivery.³⁸

PST offers an optimal test situation for the evaluation of new compounds and the detection of new biologic or molecular discriminants of either response or resistance. pCR may be used as a surrogate end point to substitute for survival and potentially provides a possibility of avoiding the arduous process of large randomized trials. In addition, tissue banking before, during, and after PST may permit the identification of undiscovered patterns of presentation of biologic or molecular discriminants that could help exclude ineffective treatments and optimize systemic regimens (Fig 1).

How Should a Diagnosis of Invasive Breast Cancer Be Confirmed Before PST?

Core biopsy and histologic examination are considered the most appropriate techniques for the detection of both invasive and noninvasive breast carcinomas. The highest diagnostic accuracy for confirming malignant disease can be reached by obtaining at least three core biopsies from various locations within the primary tumor using, at minimum, a 14-gauge needle.³⁹ In contrast to the relatively small cytologic sample obtained by fine-needle aspiration biopsy, the three \geq 14-gauge cores obtained by core biopsy should provide enough tissue to permit the performance of complex biologic studies on the tissue samples at a later time. In patients with a pCR, the initial core biopsy will be the only source of available tumor tissue; for this reason, these samples should be stored in a tumor bank for at least 10 years.

Are There Markers That Should Be Assessed Before PST?

Typing of the tumor and assessing nuclear grade on surgically excised tissue is difficult and sometimes impossible because of changes in the tumor pattern induced by PST. We recommend that tumor grade be assessed from tissue derived from the pretreatment core biopsies. In addition, because the presence of estrogen (ER) and progesterone (PgR) receptors may have an effect on the use of postsurgical endocrine therapy, we recommend that the presence of these receptors be ascertained by immunohistochemistry before PST. In addition, the number of involved axillary lymph nodes is not assessable when PST is used without axillary dissection first; this information may be requested by the patient or may be important for radiotherapy decision making for mastectomy. However, pathologic nodal status after PST is of relevant prognostic value.^{12,26} It is not yet known if there is a need for axillary (sentinel) biopsy before PST. The determination of other markers (eg, human epidermal growth factor receptor-2 or Ki67) is optional clinically or can be attempted for research purposes; this recommendation will be updated when additional information becomes available.

Which Regimen Is Recommended for PST?

There is sufficient evidence to justify the use of anthracycline-based chemotherapy regimens outside clinical trials. A minimum of three or four cycles should be given, and additional cycles may be considered for responding patients to maximize response and to improve the probability of successful breast-conservation surgery in patients with otherwise nonoperable breast cancer. As in the adjuvant setting, in which four cycles of AC are currently widely considered to be inferior treatment for women with positive nodes, there is increasing evidence that the additional use of taxanes or the use of sequential therapies as PST in operable breast cancer is superior. Both can increase the rate of clinical and pCR of the primary tumor, the proportion of patients who have successful breast-conservation surgery, and the number of patients found to have axillary nodes not involved with tumor cells (Table 3). However, to date, as noted above, only one small trial shows potential advantage for overall survival with

sequential, non-cross-resistant regimens of PST.²⁹ It is also now evident that if patients do not experience a response after three or four cycles of systemic chemotherapy, they are less likely to respond to alternative chemotherapy regimens delivered as second-line PST. This group of patients should be offered immediate surgical resection. However, because clinical responses have been observed with the second-line PST in up to 50% of the patients⁴⁰ who progress after the first regimen, an alternative approach to surgery at that point would be to proceed with a potentially non-cross-resistant second chemotherapy regimen. In this case, however, the patient must be monitored closely to avoid significant tumor progression and inoperability.

Trastuzumab and other new targeted therapies are still under investigation and should not be used outside clinical trials.

Is There a Role for Endocrine PST Alone?

Because of the lower response rates in published endocrine trials compared with response rates in chemotherapy PST trials, we cannot recommend the use of hormonal manipulation for PST as a standard of care. In the largest of such trials, which included 337 patients, a pCR was observed in only 1.5% of patients.⁴¹

Nevertheless, endocrine therapy remains attractive for patients for whom it is desirable to avoid certain chemotherapy-related adverse events. Clinical trials that evaluate endocrine PST or short-course presurgical endocrine PST in patients with hormone receptor-positive tumors may help answer questions about the endocrine-induced modulation of biologic markers.

Endocrine therapy may be considered a second choice for selected patients; for example, for elderly women with impaired organ function, for patients who are unwilling to accept the adverse events associated with chemotherapy, for those with a low performance status, or for those who are at increased surgical risk. A positive ER or PgR status (or both) is a prerequisite for this treatment approach because hormone receptor content is predictive of the efficacy of endocrine compounds. According to prospective data from one randomized PST trial⁴⁰ and several sequential phase II studies,⁴² aromatase inhibitors are more active and better tolerated than tamoxifen and thus are preferred in postmenopausal patients. At present, there are no data available about the efficacy of endocrine PST in premenopausal patients.

How Should Chemotherapy and Endocrine Treatment Combinations Be Administered?

Endocrine treatment should be added to chemotherapy according to the standard recommendations for the adjuvant therapy of breast cancer.^{1,2} All patients with ER-positive or PgR-positive tumors (or both) are candidates for adjuvant endocrine treatment. Recently, it has been demonstrated that the sequential use of tamoxifen after the end of cyclophosphamide, doxorubicin, and fluorouracil chemotherapy leads to a longer disease-free survival than simultaneous use.⁴³ This is in concordance with results showing that the concurrent use of chemotherapy and tamoxifen in PST increases toxicity without a demonstrable improvement in benefit.³⁰ Sequential treatment (ie, starting endocrine treat-

Table 4. Definitions for Response Evaluation of Primary Systemic Therapy in Breast Cancer

Clinical definition	Partial: reduction of tumor area to $\leq 50\%$ (cPR) Complete: no palpable mass detectable (cCR)
Imaging definition	No tumor visible by mammography and/or ultrasound and/or magnetic resonance imaging tomography (iCR)
Pathologic definition	Only focal invasive tumor residuals in the removed breast tissue Only in situ tumor residuals in the removed breast tissue (pCR inv) No invasive or in situ tumor cells in the removed breast tissue (pCR) No malignant tumor cells in removed breast and lymph nodes (pCR breast + nodes)

ment after surgery and completion of chemotherapy) is therefore recommended.

How, When, and How Often Should the Effect of PST Be Monitored?

The present standard of care is to carry out palpation of the primary tumor and regional lymph nodes before the start of chemotherapy and at the end of each cycle. Mammography or breast ultrasonography (or both) is optional, but either technique may be useful when the clinical response is ambiguous or to confirm progression. However, it is important to emphasize that this requires a baseline examination using the same technique (mammography or ultrasound) before PST is begun. Additional methods, such as magnetic resonance imaging or positron emission tomography of the breast, should only be used in the context of clinical trials.

Possible definitions used to report tumor response to primary systemic treatment are given in Table 4.

How Should Tumor Location Be Documented?

PST requires collaboration among the medical oncologist, cancer surgeon, and diagnostic radiologist. All three disciplines should be involved in treatment decision making and in patient follow-up during PST. Cooperation is particularly important if the patient's tumor does not respond to PST and immediate surgery is required. Close interdisciplinary patient follow-up is also required should the tumor shrink rapidly and presurgical tumor localization become difficult.

The radiation oncologist will play an important role in deciding if postoperative radiation therapy is indicated and in its planning. Preoperative external beam and brachytherapy are not established as modes of treatment in conjunction with PST. For this reason, precise documentation of the tumor location with a sketch (Fig 2) or photographs (or both) is strongly recommended. Such documentation can provide the surgeon with sufficient information to locate the tumor bed in case of complete tumor remission, and to estimate the initial tumor size in case of tumor shrinkage. Different marking procedures have been recommended in clinical trials (eg, inserting clips or coils in the center of the lesion or placing a tattoo on the skin); stereotactic location of the initial tumor area using mammography, guided by

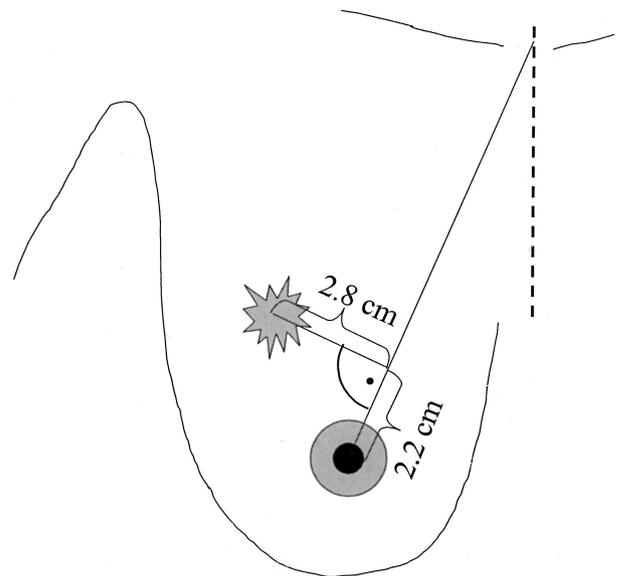


Fig 2. Proposal for identifying a palpable mass after complete clinical response by documentation of a sketch.

the baseline film, is also feasible. The complete disappearance of the tumor on clinical examination or by mammography or breast ultrasound has been a rare event until recently, but with the increasing rate of pCR, this may become more frequent, and standardized location procedures need to be developed.

How Should the Tumor Be Treated Surgically?

The aim of surgery with or without PST is to obtain clear margins of at least 1 mm at pathology examination; tumor-free margins after the use of PST should be ≥ 1 mm. It is assumed that defined tumor-free margins will result in a higher breast conservation rate. No compromise should be made in surgical margins to obtain a better cosmetic result.

Again, no significant difference has been found between PST and AST in 8-year local recurrence rates of breast cancer (randomized trials).³⁷ Patients diagnosed before the age of 40 years and those with larger tumors, high rates of tumor proliferation, or close or involved surgical margins are at higher risk for ipsilateral tumor recurrence after breast-conserving surgery.⁴⁴ This may be due to the aggressive characteristics of the primary tumor, to suboptimal surgery, or to the increased difficulty a surgeon may have when estimating tumor area after multifocal tumor shrinkage induced by PST occurs.³⁰ For these women, an increased rate of second surgical procedures has been reported.³⁵ Patients should be informed about this possible disadvantage before deciding for or against the use of PST.

How Should Tumor Tissue Be Examined by the Pathologist?

The pathologist can only provide an appropriate examination of the surgical specimen if he or she has been informed about whether PST was used. We recommend systematic sectioning perpendicular to the long axis of the specimen; random sections or a so-called orange-peel technique is not

adequate. X-rays of the specimen may help detect tumor foci not otherwise apparent. A detailed report should be given that includes the extent of the primary tumor, the presence or absence of multifocality, the extent of an intraductal component, the presence of lymphatic tumor emboli, host response, and lymph node response.

We advise that the summary report should include a reference to one of the recognized grading systems for tumor regression.⁴⁵⁻⁴⁷ The presence or absence of invasive or noninvasive tumor components should be clearly stated (Table 4). Posttreatment pathology assessment of the tumor should be completed using the tumor-node-metastasis staging system.⁴⁷

What Is the Role of Postoperative Chemotherapy After PST?

For patients with inflammatory breast cancer, it has been argued that postoperative chemotherapy is an integral part of treatment, but it is more appropriate to administer maximum chemotherapy before surgery, when its efficacy can be easily assessed. To date, there are no data that support or negate the use of postoperative chemotherapy when the response of the primary tumor or regional lymph nodes to PST is inadequate. It is not known whether the use of preoperative and postoperative chemotherapy together provide better or worse results than the results obtained from administration of all chemotherapy preoperatively.

Conclusive data on this point may become available in the near future from the National Surgical Adjuvant Breast and Bowel Project Trial B-27 or from the European Cooperative Trial in Operable Breast Cancer.^{33,35}

When and Where Should Postoperative Radiotherapy Be Administered?

Whereas radiotherapy is considered a standard part of the treatment regimen for patients with locally advanced breast cancer, in operable breast cancer, radiotherapy after PST should be administered according to the same recommendations made for those who do not receive PST.^{49,50} An indication for postmastectomy radiotherapy of the chest wall (with or without regional lymph nodes) on the basis of tumor size should be based on initial tumor size. The unfavorable prognosis associated with axillary lymph nodes shown to be involved with tumors after the completion of PST should also be taken into account. Even in patients who experience histologically complete remission, whole-breast irradiation is indicated after breast-conserving

surgery. There are no definitive data on the importance of nodal status after PST and the need for axillary radiotherapy. Treatment decisions in these situations must be made on an individual basis. Although preoperative radiotherapy improves the rate of successful breast-conservation surgery and is feasible without compromising cosmetics,⁵¹ there are sufficient data to demonstrate that radiotherapy is not a substitute for surgery; locoregional control is inadequate when the patient is treated with radiotherapy alone.⁵²

What Issues Remain to Be Resolved?

The use of preoperative PST, with the aim of improving operability, rather than postoperative systemic therapy is only the first step in exploring the advantages of primary (preoperative) treatment. Future research should concentrate on the way in which PST, acting as an *in vivo* chemosensitivity test, can be used to benefit each patient. The selection of patients for a specific treatment that offers them a high probability of achieving pCR is crucial, and PST is an ideal tool with which to assess predictive clinical and pathologic factors. Examining tumor tissue before, during, and after PST is possible using modern technology such as immunohistochemistry, fluorescence *in situ* hybridization, DNA microarrays, tissue microarrays, or proteomics (Fig 1).⁵³

New compounds directed against specific molecular targets associated with the tumor should be explored in the primary therapy setting. The use of such compounds for PST may demonstrate their effect and proof of concept that the target may serve as a surrogate marker for either clinical benefit or disadvantage, which could lead to the development of new drugs that have demonstrated activity against breast cancer.

PST is considered the standard of care for nonoperable, locally advanced breast cancer. For operable breast cancer, PST provides additional opportunity for breast-conserving surgery. Current data indicate that pCR may be used as a surrogate indicator for the beneficial effect of PST on both disease-free and overall survival. On the basis of the biologic characteristics of a tumor and differences in the response to systemic treatment, PST should be regarded as a tool that can be used to individualize systemic therapy for patients with breast cancer.

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APPENDIX

The appendix is included in the full text version of this article only, available on-line at www.jco.org. It is not included in the PDF version.

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International expert panel on the use of primary (preoperative) systemic treatment of operable breast cancer: review and recommendations. AU.Â Primary systemic therapy (PST) represents the standard of care in patients with locally advanced breast cancer. In addition, there is increasing information on PST in operable breast disease that supports the use of PST in routine practice. However, current regimens and techniques vary.Â Recommendations are made regarding terminology, indications, regimen, diagnosis before treatment, monitoring of efficacy, tumor localization, surgery, pathologic evaluation, and postoperative treatment. AD. Department of Gynecology and Obstetrics, Goethe University, Frankfurt am Main, Germany. M.Kaufmann@em.uni-frankfurt.de. PMID. Neoadjuvant (primary systemic) treatment is the standard treatment for locally advanced breast cancer and a standard option for primary operable disease.Â @article{Kaufmann2006RecommendationsFA, title={Recommendations from an international expert panel on the use of neoadjuvant (primary) systemic treatment of operable breast cancer: an update.}, author={Manfred Kaufmann and Gabriel N. Hortobagyi and Aron Goldhirsch and Suzy M. E. Scholl and Andreas Makris and Pinuccia Valagussa and Jens-Uwe Blohmer and Wolfgang Eiermann and Raimund Jackesz and Walter Jonat and Sebastian. Aulmann and Marcus Schmidt and William A. Jr.