Exp Oncol 2013
35, 4, 253–257

Experimental ONCOLOGY

POSITRON EMISSION TOMOGRAPHY/COMPUTED TOMOGRAPHY IN LOCALLY ADVANCED BREAST CANCER

E. Ozkan

Department of Nuclear Medicine, Ankara University School of Medicine, Ankara 06590, Turkey

Locally advanced breast cancer (LABC) is a relatively small group of breast cancer, but is significant because it carries a higher risk of locoregional recurrence and distant metastasis. The accepted approach for these patients is neoadjuvant chemotherapy before surgery as determining the response to therapy in the early stages is of critical importance in respect of the approach taken to the disease. Positron emission tomography/computed tomography (PET/CT) using fluorine-18-fluorodeoxyglucose (^{18}F-FDG) is currently used for staging, restaging and response monitoring in breast cancer. The areas of use of FDG PET/CT in LABC can be summarised as the evaluation of response to neoadjuvant chemotherapy in the early stage in particular, and the determination of unexpected areas of metastasis not detected by standard imaging techniques. There are current ongoing studies on promising new PET radiopharmaceuticals apart from FDG.

Key Words: **locally advanced breast cancer, PET/CT, primary staging, restaging, therapy response.**

INTRODUCTION

Breast cancer is the most commonly diagnosed cancer in women. About 5–10% of newly diagnosed breast cancer cases present with locally advanced disease [1, 2]. Locally advanced breast cancer (LABC) is characterized by a primary tumor larger than 5 cm, skin or chest wall involvement and/or the presence of fixed axillary lymph node metastases. LABC has a higher incidence of locoregional recurrence and distant metastases, which causes a poor prognosis [3, 4]. Nowadays neoadjuvant chemotherapy (NACT) before surgery is increasingly used in the management of LABC. NACT has been used in patients with LABC to reduce the tumor volume, which allows breast-conserving surgery or operability for previously inoperable breast cancer patients, and to eliminate occult distant metastases [5–7]. However, there has been no significant improvement in prognosis with the use of NACT [8, 9]. On the other hand, early determination of patients who do not respond to NACT allows them to be protected from unnecessary toxic effects. Different treatment choices can be applied to these patients.

Generally, the Response Evaluation Criteria in Solid Tumors (RECIST) [10] has been used to evaluate the response to treatment. This criteria is based on anatomic imaging modalities, such as computed tomography (CT) and magnetic resonance imaging (MRI), which are used to measure the maximum tumor diameter. Response criteria is defined as a decrease in the tumor diameter of at least 30% [10]. However, several cycles of chemotherapy are necessary for the cytotoxic effect which will cause a reduction in the size of the tumour. It is not possible to evaluate the chemosensitivity in the early stage by RECIST criteria.

In the evaluation of response to chemotherapy, the use of functional imaging such as positron emission tomography (PET) is useful to overcome the limitations of anatomic imaging modalities. PET with fluorine-18-fluorodeoxyglucose (^{18}F-FDG) is used in various cancers for staging, evaluating the response to treatment and also restaging when there is suspicion of recurrence [11]. The use of CT, particularly with hybrid PET/CT systems, increases the success of functional evaluation. Nowadays there are studies with promising results that early stage response to chemotherapy can be evaluated and more correct staging can be applied to LABC patients with the use of PET/CT systems with FDG [12–15]. This review aimed to examine the contribution and significance of the use of FDG PET/CT in the evaluation of LABC patients and also to consider the clinical contribution of blood flow and tumour proliferation agents which will be used more frequently in the near future.

PRIMARY STAGING

Correct staging of breast cancer is important in deciding the most appropriate therapy option. However, systemic staging is not indicated for early breast cancer in the absence of symptoms. FDG PET and PET/CT are not recommended for routine staging of breast cancer particularly in the early stage because of low sensitivity in detecting small lesions and moderately increased uptake in primary tumor [16].

In the axillary staging of cases with small primary tumours, PET sensitivity has been found to have a limited value of approximately 20% [17–19]. In the differentiation in terms of sentinel lymph node dissection of patients with clinically negative lymph nodes, FDG PET is not sufficiently accurate [20, 21]. However, FDG PET/CT is a good method for the evaluation of the spread of the disease in cases with locally advanced disease who will undergo NACT [22]. It can identify

Received: March 22, 2013.
Correspondence: Fax: +90 312 362 08 97
E-mail: ozkanelgin@yahoo.com

Abbreviations used: CT – computed tomography; ^{18}F – fluorine-18; FDG – fluorodeoxyglucose; FLT – fluoro-L-thymidine; LABC – locally advanced breast cancer; MRI – magnetic resonance imaging; NACT – neoadjuvant chemotherapy; PET/CT – positron emission tomography/computed tomography; RECIST – Response Evaluation Criteria in Solid Tumors; USG – ultrasonography.

unsuspected regional nodal disease and/or distant metastases when used in addition to standard staging modalities [16]. Today FDG PET is the most sensitive method to identify parasternal and mediastinal metastatic lymph nodes, which are detected more frequently in LABC.

EVALUATION OF THERAPY RESPONSE

The routine application for LABC patients is NACT and then surgery. The tumour response following NACT has prognostic significance for disease-free survival and overall survival time [22]. Patients in whom full response is observed macroscopically following chemotherapy have a significantly better prognosis than patients with residual disease [23]. In addition, those with minimal residual disease have a significantly longer disease-free survival and overall survival than those with gross residual disease [22, 23]. Clinical response is observed in approximately 70% of patients following NACT, while partial or full pathological response is seen in 20–30% of patients [2, 22, 24]. No definite relationship has been found between pathological response and clinical response. Even if there is no clinical response due to the presence of scar tissue, full pathological response may be seen because of the disappearance of tumour cells. Clinical examination alone is not reliable in the evaluation of response to chemotherapy [25, 26].

Changes in tumour size are measured by anatomic imaging methods, such as CT, MRI and ultrasonography (USG), which are currently used in the evaluation of response to therapy. A reduction in tumour size of at least 30% is the acceptable criteria for response [10]. However, to be able to see a tumour response radiologically, several cycles of chemotherapy are necessary. It does not seem to be possible by radiological imaging methods to predict response to therapy in the early stage and thus avoid unecessary chemotherapy application. The relationship between radiological tumour response and pathological response is weak. Anatomic imaging methods do not allow for the differentiation of viable tumour tissue and fibrotic tissue [27].

Functional imaging with FDG-PET may give an idea about the metabolic tumour cell response before anatomical response occurs [24]. FDG-PET is especially useful in the determination of metabolically active tumours which will primarily benefit from NACT [15]. Following a few cycles of chemotherapy, reduction in FDG uptake is a strong indicator for response [15]. To evaluate response to therapy in breast cancer, PET images taken in different cycles are evaluated; basal, early-therapy (after the first cycle of therapy), mid-therapy and post-therapy [12–14, 28–31]. PET sensitivity and specificity for the evaluation of response to therapy has been reported in literature at wide ranges of 39–100% and 74–100%, respectively. This can be explained by the patients included in studies not being homogenous, not performing PET scans with standard protocols, using different SUV cutoff values in the evaluation and using different pathological criteria [28]. Rousseau et al. investigated the efficacy of FDG-PET for evaluating early response to NACT in 64 patients with stage II and III breast cancer, the FDG-PET scans were taken after the 1st, 2nd, 3rd and 4th courses of chemotherapy and they reported that early response to NACT may be best evaluated after two courses of chemotherapy [14]. Similarly, Kumar et al. reported that after the second cycle of NACT in LABC patients, those responding to therapy can be differentiated from non-responders [28]. In the same study, results of PET/CT, clinical examination and CT findings were compared and the accuracy rates were found to be 87; 39 and 56% respectively. As PET/CT allows for metabolic/functional evaluation, it has been reported that PET/CT can give an idea of response to therapy before the onset of structural changes which can be determined by anatomic imaging methods [28]. It has been emphasised that clinical examination results are not sufficient due to the changes in breast tissue after chemotherapy [28]. In predicting the pathological response following NACT, FDG uptake changes measured in midtherapy PET/CT are mainly used. Generally, a 50% or greater reduction in midtherapy FDG uptake has been accepted as a indicator of response to NACT in studies [28–35]. However, many different cutoff values for percentage SUV changes have been reported, with threshold values varying between 20–88% to be used in the differentiation of responders [12–14, 29, 30]. Kumar et al. accepted a 50% reduction in basal SUV as the SUV cutoff value to differentiate between responders and non-responders to therapy following 2 cyles of NACT, and found PET sensitivity and specificity as 93% and 75%, respectively [28]. In a study by Rousseau et al., a 60% reduction in basal SUV was accepted as the threshold value, and PET sensitivity and specificity following 2 cycles of chemotherapy was reported as 89 and 95%, respectively [14]. One of the critical points in the evlauation of response to therapy with FDG PET is the fact that there is a relationship between the observation of FDG uptake and the presence of residual disease or alive tumour cells, but the absence of FDG uptake is not always a true indicator of full pathological response [29, 36, 37]. This is especially true for axillary lymph node metastasis and the sensitivity of PET for evaluation of axillary nodule metastasis in the post-therapy period is low [38].

Other PET radiopharmaceuticals, apart from FDG, used in the evaluation of response following chemotherapy include the tumour blood flow tracer, ^{15}O-water and the tumour proliferation agent, ^{18}F-fluoro-L-thymidine (FLT). Although there are a relatively limited number of studies related to these agents, in studies using ^{15}O-water to evaluate tumour blood flow, it has been reported that in patients with no significant reduction in tumour blood flow following treatment, there was an increase in recurrence risk and mortality rates [39]. Tumour blood flow and metabolism are known to show considerable variations in LABC patients [32, 34, 39]. It has been reported that the flow-metabolism mis-

match (high FDG metabolism in proportion to blood flow) observed in tumours in the pre-treatment period is related to treatment resistance and increased risk of early relapse [34, 40]. In a study by Specht et al., evaluating tumour metabolism and blood flow changes following treatment according to the tumour subtype in 71 LABC patients, flow-metabolism mismatch was more often seen in triple negative (oestrogen receptor, progesterone receptor, and HER2-negative) breast cancer patients and this was reported to indicate a poor response to therapy [41].

The PET agent currently used in the evaluation of tumour proliferation is ^{18}F-FLT. Thymidine uptake is a specific indicator of tumour cell proliferation. In primary and metastatic breast cancers, large primary tumours with metastatic axillary lymph nodes in particular, are defined by increased FLT uptake [42]. It has been reported that the effect of chemotherapy can be predicted by FLT-PET two weeks after one cycle of chemotherapy has been completed [43]. High glucose metabolism is not always correlated with increased tumour proliferation [44]. Therefore, an increased number of studies which evaluate tumour glucose metabolism and cellular proliferation together would be helpful to predict response to chemotherapy for different tumour characteristics.

RESTAGING

The correct evaluation of the spread of the disease is important in the choice of a more effective treatment strategy and to obtain successful results. FDG-PET has great importance in defining the correct treatment method in recurrent or advanced breast cancer patients [44]. Raised tumour markers in particular may detect recurrence, apart from occult disease, in suspicious cases or where conventional methods or physical examination results are negative [45, 46]. It is useful in previously treated or symptomatic breast cancer patients for the differentiation of secondary effects with locoregional recurrence of radiotherapy or surgery [44, 47]. In cases where there is suspicion of locoregional recurrence, the determination of the internal mammarian node is a facilitating factor for the spread of the disease to a wider area [48, 49]. In the determination of the internal mammarian node, PET sensitivity and specificity have been found to be 85 and 90%, respectively, and CT sensitivity and specificity 50 and 83%, respectively [50]. It is known that locoregional recurrence and distant metastasis are seen more often in LABC. One of the most frequent areas of metastasis in breast cancer is the bones [44]. Although bone scintigraphy is a sensitive method of determining bone metastases, it is not sufficient to detect purely osteolystic or lesions confined to the bone marrow cavity [51]. FDG PET seems to be an adequate method in the determination of osteolytic metastases [52]. This shows the complementary role of bone scintigraphy and FDG PET in the determination of bone metastasis in breast cancer.

CONCLUSIONS

The role of PET/CT in LABC can be summarised under 4 headings. Firstly, that FDG-PET and PET/CT are not recommended for routine staging of breast cancer, particularly in the early stage. However, FDG PET/CT is a useful method to evaluate the extent of the disease in patients with LABC. It can identify unsuspected regional nodal disease such as parasternal and mediastinal lymph nodes which are detected more frequently in LABC. Secondly, NACT has become the standard therapy modality for patients with LABC. Tumour response following NACT has prognostic importance for disease-free survival and overall survival duration. Functional imaging with FDG-PET can indicate the tumour cell response before the radiological tumour response can be detected. A reduction in FDG uptake following a few cycles of chemotherapy is a strong indicator of response. Thirdly, apart from tumour glucose metabolism, the evaluation of blood flow and cell proliferation together may provide more information about the response to chemotherapy and tumour biology. Lastly, FDG PET is generally more sensitive than conventional methods in the determination of locoregional recurrence and distant metastases. It is therefore an appropriate method which can be used for the accurate determination of the spread of the disease.

CONFLICT OF INTEREST

There is no conflict of interest.

REFERENCES

1. **Bonadonna G, Valagussa P, Zucali R, *et al.*** Primary chemotherapy in surgically resectable breast cancer. CA Cancer J Clin 1995; **45:** 227–43.

2. **van der Hage JA, van de Velde CJ, Julien JP, *et al.*** Preoperative chemotherapy in primary operable breast cancer: results from the European Organization for Research and Treatment of Cancer trial 10902. J Clin Oncol 2001; **19:** 4224–37.

3. **Haagensen CD, Stout AP.** Carcinoma of the breast — I; Results of treatment. Ann Surg 1942; **116:** 801–15.

4. **Haagesen CD, Stout AP.** Carcinoma of the breast — II; Criteria of operability. Ann Surg 1943; **118:** 859–70.

5. **Fisher B, Bryant J, Wolmark N, *et al.*** Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. J Clin Oncol 1998; **16:** 2672–85.

6. **Moneer M, Ismael S, Khaled H, *et al.*** A new surgical strategy for breast conservation in locally advanced breast cancer that achieves a good locoregional control rate: preliminary report. Breast 2001; **10:** 220–4.

7. **Pinedo HM, de Gruijl TD, van Der Wall E, *et al.*** Biological concepts of prolonged neoadjuvant treatment plus GM-CSF in locally advanced tumors. Oncologist 2000; **5:** 497–500.

8. **Clavel M, Catimel G.** Breast cancer: Chemotherapy in the treatment of advanced disease. Eur J Cancer 1993; **29A:** 598–604.

9. **Fisher B, Brown A, Mamounas E, *et al.*** Effect of preoperative chemotherapy on loco-regional disease in women with operable breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-18. J Clin Oncol 1997; **15:** 2483–93.

10. **Therasse P, Arbuck SG, Eisenhauer EA, *et al.*** New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 2000; **92:** 205–16.

11. **Delbeke D, Coleman RE, Guiberteau MJ, *et al.*** Procedure guideline for tumor imaging with ^{18}F-FDG PET/CT. J Nucl Med 2006; **47:** 885–95.

12. **Schelling M, Avril N, Nahrig J, *et al.*** Positron emission tomography using [^{18}F]fluorodeoxyglucose for monitoring primary chemotherapy in breast cancer. J Clin Oncol 2000; **18:** 1689–95.

13. **Smith IC, Welch AE, Hutcheon AW, *et al.*** Positron emission tomography using [^{18}F]-fluorodeoxy-D-glucose to predict the pathologic response of breast cancer to primary chemotherapy. J Clin Oncol 2000; **18:** 1676–88.

14. **Rousseau C, Devillers A, Sagan C, *et al.*** Monitoring of early response to neoadjuvant chemotherapy in stage II and stage III breast cancer by [^{18}F] fluorodeoxyglucose positron emission tomography. J Clin Oncol 2006; **24:** 5366–72.

15. **Schwarz-Dose J, Untch M, Tiling R, *et al.*** Monitoring primary systemic therapy of large and locally advanced breast cancer by using sequential positron emission tomography imaging with [^{18}F]fluorodeoxyglucose. J Clin Oncol 2009; **27:** 535–41.

16. **Carlson RW, Allred DC, Anderson BO, *et al.*** Breast cancer: clinical practice guidelines in oncology. J Natl Comp Canc Netw 2009; **7:** 122–192.

17. **Fehr MK, Hornung R, Varga Z, *et al.*** Axillary staging using positron emission tomography in breast cancer patients qualifying for sentinel lymph node biopsy. Breast 2004; **10:** 89–93.

18. **Barranger E, Grahek D, Antoine M, *et al.*** Evaluation of fluorodeoxyglucose positron emission tomography in the detection of axillary lymph node metastases in patients with early-stage breast cancer. Ann Surg Oncol 2003; **10:** 622–7.

19. **Kelemen PR, Lowe V, Phillips N.** Positron emission tomography and sentinel lymph node disection in breast cancer. Clin Breast Cancer 2002; **3:** 73–77.

20. **Veronesi U, De Cicco C, Galimberti VE, *et al.*** A comparative study on the value of FDG-PET and sentinel node. Ann Oncol 2007; **18:** 473–8.

21. **Gil-Rendo A, Zornoza G, Garcia-Velloso MJ, *et al.*** Fluorodeoxyglucose positron emission tomography with sentinel lymph node biopsy for evaluation of axillary involvement in breast cancer. Br J Surg 2006; **93:** 707–12.

22. **Bonadonna G, Valagussa P, Brambilla C, *et al.*** Primary chemotherapy in operable breast cancer: eight-year experience at the Milan Cancer Institute. J Clin Oncol 1998; **16:** 93–100.

23. **Machiavelli M, Romero A, Perez K, *et al.*** Prognostic significance of pathologic response of primary tumor and metastatic axillary lymph nodes after neoadjuvan chemotherapy for locally advanced breast carcinoma. Cancer 1998; **4:** 125–31.

24. **Fisher ER, Wang J, Bryant J, *et al.*** Pathobiology of preoperative chemotherapy: findings from the National Surgical Adjuvant Breast and Bowel (NSABP) protocol B-18. Cancer 2002; **95:** 681–95.

25. **Herrada J, Iyer RB, Atkinson EN, *et al.*** Relative value of physical examination, mammography, and breast sonography in evaluating the size of the primary tumor and regional lymph node metastases in women receiving neoadjuvant chemotherapy for locally advanced breast carcinoma. Clin Cancer Res 1997; **3:** 1565–69.

26. **Helvie MA, Joynt LK, Cody RL, *et al.*** Locally advanced breast carcinoma: accuracy of mammography *versus* clinical examination in the prediction of residual disease after chemotherapy. Radiology 1997; **198:** 327–32.

27. **Vinnicombe SJ, MacVicar AD, Guy RL, *et al.*** Primary breast cancer: mammographic changes after neoadjuvant chemotherapy, with pathologic correlation. Radiology 1996; **198:** 333–40.

28. **Kumar A, Kumar R, Seenu V, *et al.*** The role of ^{18}F-FDG PET/CT in evaluation of early response to neoadjuvant chemotherapy in patietns with locally advanced breast cancer. Eur Radiol 2009; **19:** 1347–57.

29. **Kim SJ, Kim SK, Lee ES, *et al.*** Predictive value of [^{18}F]FDG PET for pathological response of breast cancer to neo-adjuvant chemotherapy. Ann Oncol 2004; **15:** 1352–57.

30. **Wahl RL, Zasadny K, Helvie M, *et al.*** Metabolic monitoring of breast cancer chemohormonotherapy using positron emission tomography: initial evaluation. J Clin Oncol 1993; **11:** 2101–11.

31. **Tiling R, Linke R, Untch M, *et al.*** ^{18}F-FDG PET and ^{99m}Tc-sestamibi scintimammography for monitoring breast cancer response to neoadjuvant chemotherapy: a comparative study. Eur J Nucl Med 2001; **28:** 711–20.

32. **Mankoff DA, Dunnwald LK, Gralow JR, *et al.*** Changes in blood flow and metabolism in locally advanced breast cancer treated with neoadjuvant chemotherapy. J Nucl Med 2003; **44:** 1806–14.

33. **Mankoff DA, Eubank WB.** Current and future use of positron emission tomography (PET) in breast cancer. J Mammary Gland Biol Neoplasia 2006; **11:** 125–36.

34. **Mankoff DA, Dunnwald LK, Gralow JR, *et al.*** Blood flow and metabolism in locally advanced breast cancer: relationship to response to therapy. J Nucl Med 2002: **43:** 500–9.

35. **Mankoff DA, Dunnwald LK, Gralow JR, *et al.*** Monitoring the response of patients with locally advanced breast carcinoma to neoadjuvant chemotherapy using [technetium-99m]-sestamibi scintimammography. Cancer 1999; **85:** 2410–23.

36. **Burcombe RJ, Makris A, Pittam M, *et al.*** Evaluation of good clinical response to neoadjuvant chemotherapy in primary breast cancer using [^{18}F]-fluorodeoxyglucose positron emission tomography. Eur J Cancer 2002; **38:** 375–9.

37. **Bassa P, Kim EE, Inoue T, *et al.*** Evaluation of preoperative chemotherapy using PET with fluorine-18-fluorodeoxyglucose in breast cancer. J Nucl Med 1996; **37:** 931–8.

38. **Rosen EL, Eubank WB, Mankoff DA.** FDG PET, PET/CT, and breast cancer imaging. Radiographics 2007; **27:** 215–29.

39. **Dunnwald LK, Gralow JR, Ellis GK, *et al.*** Tumor metabolism and blood flow changes by positron emission tomography: relation to survival in patients treated with neoadjuvant chemotherapy for locally advanced breast cancer. J Clin Oncol 2008; **26:** 4449–57.

40. **Eby P, Partridge SC, White S.** Metabolic and vascular features of dynamic contrast-enhanced breast magnetic resonance imaging and (15)O-water positron emission tomography blood flow in breast cancer. Acad Radiol 2008; **15:** 1246–54.

41. **Specht J, Kurland BF, Montgomery SK, *et al.*** Tumor metabolism and blood flow as assessed by positron emission tomography varies by tumor subtype in locally advanced breast cancer. Clin Cancer Res 2010; **16:** 2803–10.

42. **Been LB, Elsinga PH, de Vries DM, *et al.*** Positron emission tomography in patients breast cancer using ^{18}F-3-deoxy-3-fluoro-L-thymidine (^{18}F-FLT): a pilot study. Eur J Surg Oncol 2006; **32:** 39–43.

43. **Pio BS, Park CK, Pietras R, *et al.*** Usefulness of 3-[F-18]fluoro-3-deoxythymidine with positron emission tomography in predicting breast cancer response to therapy. Mol Imaging Bio 2006; **8:** 36–42.

44. **Eubank WB, Mankoff DA.** Current and future uses of positron emission tomography in breast cancer imaging. Semin Nucl Med 2003; **34:** 36–42.

45. **Liu CS, Shen YY, Lin CC, *et al.*** Clinical impact of [(18) F]FDG-PET in patients with suspected recurrent breast cancer based on asymptomatically elevated tumor marker serum levels: a preliminary report. Jpn J Clin Oncol 2002; **32**: 244–7.

46. **Suárez M, Pérez-Castejón MJ, Jiménez A, *et al.*** Early diagnosis of recurrent breast cancer with FDG-PET in patients with progressive elevation of serum tumor markers. Q J Nucl Med 2002; **46:** 113–21.

47. **Eubank WB, Mankoff DA, Schmiedl UP, *et al.*** Imaging of oncologic patients: benefit of combined CT and [F-18]-fluorodeoxyglucose positron emission tomography scan interpretation in the diagnosis of malignancy. AJR 1998; **171:** 1103–10.

48. **Cody HS 3rd, Urban JA.** Internal mammary node status: a major prognosticator in axillary node-negatice breast cancer. Ann Surg Oncol 1995; **2:** 32–7.

49. **Bellon JR, Gralow JR, Livingston RB, *et al.*** Evaluation of the internal mammary (IM) lymph nodes by FDG-PET in locally advanced breast cancer (LABC). Am J Clin Oncol 2004; **27:** 407–10.

50. **Eubank WB, Mankoff DA, Takasugi J, *et al.*** 18-fluorodeoxyglucose positron emission tomography to detect mediastinal or internal mammary metastases in breast cancer. J Clin Oncol 2001; **19:** 3516–23.

51. **Nielsen OS, Munro AJ, Tannock IF.** Bone metastases: pathophysiology and management policy. J Clin Oncol 1991; **9:** 509–24.

52. **Cook GJ, HoustonS, Rubens R, *et al.*** Detection of bone metastases in breast cancer by ^{18}FDG-PET: differing metabolic activity in osteoblatic and osteolytic lesions. J Clin Oncol 1998; **16:** 3375–9.