Clin Transl Oncol (2010) 12:735-741
DOI 10.1007/s12094-010-0588-3

CLINICAL GUIDES IN ONCOLOGY

SEOM clinical guidelines for the treatment of non-small-cell lung cancer: an updated edition

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Received: 6 July 2010 / Accepted: 7 September 2010

Special announcement

These guidelines have been updated from the previous ones published in 2009: SEOM guidelines for the management of non-small-cell lung cancer (NSCLC) [1], taking into account the new recommendations included during this year in our clinical practice consideration, e.g., new TNM staging system, new indications for therapy especially for advanced disease, etc.

Abstract The purpose of this article is to provide updated recommendations for the diagnosis and treatment of patients non–small-cell lung cancer (NSCLC). The staging system for lung cancer has recently been revised by the International Association for Study of Lung Cancer and patients with NSCLC shall now be staged according to the UICC system 7th edition. Recommendations for treatment were based on treatment strategies that improve overall survival. In functionally fit patients with stage I–II disease surgical resection is recommended. Four cycles of adjuvant cisplatin-based chemotherapy is recommended in patients with pathologic stage II–III. For patients with stage IIIA and non-bulky mediastinal lymph node survival was significantly improved with induction chemotherapy plus surgical resection. Patients with unresectable or bulky stage IIIA and those with stage IIIB, should be treated with platinum-based chemotherapy and thoracic radiotherapy. For patients with metastatic disease and performance status of 0 or 1, a platinum-based two-drug combination of cytotoxic drugs is recommended. Nonplatinum cytotoxic doublets are acceptable for patients with contraindications to platinum therapy. For elderly patients and those with performance status of 2, a single cytotoxic drug is sufficient. Stop first-line cytotoxic chemotherapy at disease progression or after four cycles in patients who are not responding to treatment. Stop two-drug cytotoxic chemotherapy at six cycles even in patients who are responding to therapy. The first-line use of gefitinib may be recommended for patients with known epidermal growth factor receptor *(EGFR)* mutation; for negative or unknown *EGFR* mutation status, cytotoxic chemotherapy is preferred. Bevacizumab is recommended with platinum-based chemotherapy, except for patients with certain clinical characteristics. Maintenance therapy with pemetrexed or erlotinib increases survival in patients who did not progress after 4 cycles of a platinum based chemotherapy. Docetaxel, erlotinib, gefitinib, or pemetrexed is recommended as second-line therapy. Erlotinib is recommended as third-line therapy for patients who have not received prior erlotinib or gefitinib. Data are insufficient to recommend the routine third-line use of cytotoxic drugs.

Keywords Lung cancer · Guideline · Recommendation

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Introduction

Lung cancer is currently the most common malignancy and also the leading cause of mortality related to cancer in the world [2]. The crude incidence of lung cancer in the EU is 52.5/100,000/year and the mortality 48.7/100,000/year. Among men the rates are 82.5 and 77.0/100,000/year; among women 23.9 and 22.3/100,000/year, respectively. NSCLC accounts for 80% of all cases. In Spain, there were 16,879 deaths in men, with a mean age of 68 years, and 2634 deaths in women, with a mean age of 66 years. The incidence of lung cancer in Spain was 68.3/100,000 among men and 13.8/100,000 among women, according to the latest data published in 2006 by the *Instituto Nacional de Estadística*. About 90% of lung cancer mortality among men (and 80% among women) is attributable to smoking.

Diagnosis and staging

Diagnosis

Pathologic lung cancer diagnosis should be made according to the WHO classification. Histologic or cytologic specimens can be obtained from the primary tumour, lymph nodes or metastatic sites.

After the initial diagnosis, accurate staging is crucial for determining the appropriate approach and for tailoring therapy to each individual patient. In NSCLC patients the following staging work-up is recommended [3] (Table 1):

- Complete history and physical examination.
- Computerised tomography (CT) scan of the chest and upper abdomen.
- Magnetic resonance imaging (MRI) or CT scan of the brain if there are abnormal neurologic findings.
- Bone scan in the presence of bone pain, elevated serum calcium or elevated alkaline phosphatase levels.

In patients in which potentially radical treatment is contemplated, the following should be considered:

- Whole-body FDG-positron emission tomography (PET) scan.
- In the case of abnormal results on PET scan with mediastinal lymph node enlargement, a biopsy of mediastinal lymph node is recommended.
- Invasive procedures may be omitted in patients with peripheral tumours and negative mediastinal and hilar nodes on PET scan.
- MRI or CT scan of the brain may be considered.

In patients with otherwise potentially radically treatable disease:

- In the presence of pleural or pericardial effusions, cytology of pleural/pericardial effusions must be performed.
- In patients with a single metastatic lesion, biopsy should be recommended to prove metastatic disease.

Staging system

The staging system for lung cancer has recently been revised through the International Association for Study of Lung Cancer (IASLC). Patients with NSCLC shall now be staged according to the UICC system (7th edition) and grouped into the stage categories shown in Tables 2 and 3 [4].

Treatment

Stage I–II (Fig. 1)

- In patients with stage I–II disease a multidisciplinary evaluation by a Tumor Committee is recommended to establish the best strategy.
- In functionally fit patients with stage I–II disease, surgical resection is recommended (lobectomy/pneumonectomy with lymphadenectomy). A careful preoperative physiologic assessment will be useful to identify those patients who are at increased risk of postoperative complications with standard lung cancer resection. If the FEV1 is >80% of predicted normal and there is no evidence of either undue dyspnoea on exertion or interstitial disease, the patient is suitable for resection, including pneumonectomy. Otherwise, further tests to evaluate lung function are recommended.
- Radical radiotherapy is to be considered in patients unfit for surgery. Until recently, conventional radiation therapy was the only alternative curative treatment option for patients who were unfit for surgery.

Table 1 Diagnosis and staging

Histologic or cytologyc specimens
Complete history and physical examination/blood analyses
CT scan of the chest/upper abdomen
MRI of CT-scan of the brain if abnormal neurologic findings
Bone scan in presence of bone pain, elevated serum calcium or alkaline phosphatase levels
In patients in which potentially radical treatment is contemplated:
PET
Invasive mediastinal procedures for mediastinum staging
MRI or CT scan of the brain may be considered

Table 2 TNM classification

T (primary tumor)	
TX	Primary tumour cannot be assessed, or tumour proven by the presence of malignant cells in sputum or bronchial washings but not visualised by imaging or bronchoscopy
T0	No evidence of primary tumour
Tis	Carcinoma *in situ*
T1	Tumour ≤3 cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)
T1a	Tumour ≤2 cm in greatest dimension
T1b	Tumour >2 cm but ≤3 cm in greatest dimension
T2	Tumour >3 cm but ≤7 cm or tumor with any of the following reatures (T2 tumors with these features are classified T2a if ≤5 cm) Involves main bronchus ≥2 cm distal to the carina Invades visceral pleura Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
T2a	Tumour >3 cm but ≤5 cm in greatest dimension
T2b	Tumour >5 cm but ≤7 cm in greatest dimension
T3	Tumour >7 cm or one that directly invades any of the following: chest wall (including superior sulcus tumours), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; or tumour in the main bronchus <2 cm distal to the carina but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung or separate tumour nodules(s) in the same lobe
T4	Tumour of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, carina; separate tumour nodule(s) in a different ipsilateral lobe
N (regional lymph nodes)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)
M (distant metastasis)	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
M1a	Separate tumour nodule(s) in a contralateral lobe; tumour with pleural nodules or malignant pleural (or pericordial) effusion
M1b	Distant metastasis

Table 3 Stage grouping

Occult carcinoma	TX	N0	M0
Stage 0	Tis	N0	M0
Stage IA	T1a,b	N0	M0
Stage IB	T2a	N0	M0
Stage IIA	T1a,b	N1	M0
	T2a	N1	M0
	T2b	N0	M0
Stage IIB	T2b	N1	M0
	T3	N0	M0
Stage IIIA	T1, T2	N2	M0
	T3	N1, N2	M0
	T4	N0, N1	M0
Stage IIIB	T4	N2	M0
	Any T	N3	M0
Stage IV	Any T	Any N	M1a,b

At present, the results from the use of stereotactic radiation therapy are promising in patients who are unfit for surgery.

– Nearly half of all patients who undergo surgical resection for early-stage NSCLC will develop recurrent disease. The usefulness of adjuvant chemotherapy after surgical resection in the early stage is now well established. A number of randomised trials have demonstrated the efficacy of platinum-based chemotherapy [5–9]. In the LACE meta-analysis, individual patient data were collected from the five largest randomised trials of cisplatin-based chemotherapy in completely resected patients conducted after the 1995 meta-analysis (including a total of 4584 patients). In this meta-analysis, very few patients with stage IA disease were evaluated. With a median follow-up of 5.2 years, the overall hazard ratio (HR) of death was 0.89 (p=0.005), corresponding to a 5-year absolute benefit from chemotherapy of 5.4%. The degree of benefit varied with stage; HR for stage IA=1.4, HR for stage IB=0.93, HR for stage II=0.83 and HR for stage III=0.83 [10].
– Therefore, the recommendations for adjuvant chemotherapy according to pathologic stage are as follows:
  • Adjuvant chemotherapy is not recommended in stage IA disease.

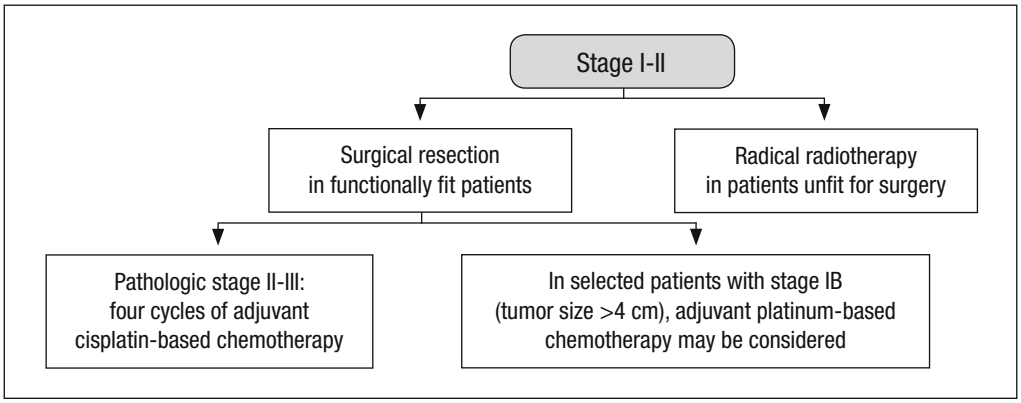


Fig. 1 Treatment algorithm for stage I-II

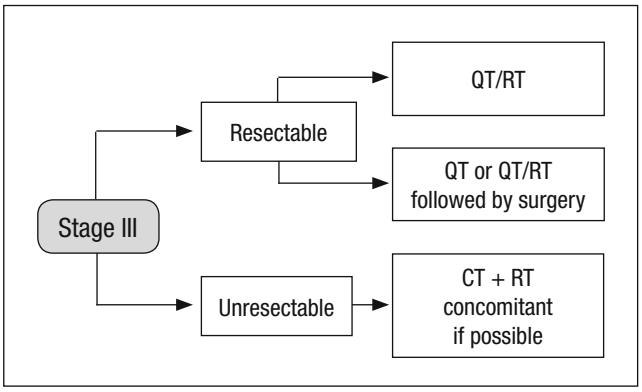


Fig. 2 Treatment algorithm for stage III

  - Four cycles of adjuvant cisplatin-based chemotherapy (a doublet combination) is recommended in patients with pathologic stage II–III.
  - Cisplatin-based chemotherapy may be considered in selected patients with stage IB disease.
- Post-operative radiotherapy is not recommended in patients with complete resection and pathologic stage I–II disease. Post-operative radiotherapy may be considered after adjuvant chemotherapy in selected patients with stage IIIAN2, although its precise contribution is yet to be defined.
- In specimens from resected patients, numerous molecular markers are being examined to see whether they can play a role in deciding which patients should be treated with adjuvant chemotherapy and which drugs should be used. Adjuvant trials addressing the impact of molecular markers in treatment decisions are a high priority in the early-stage NSCLC setting.

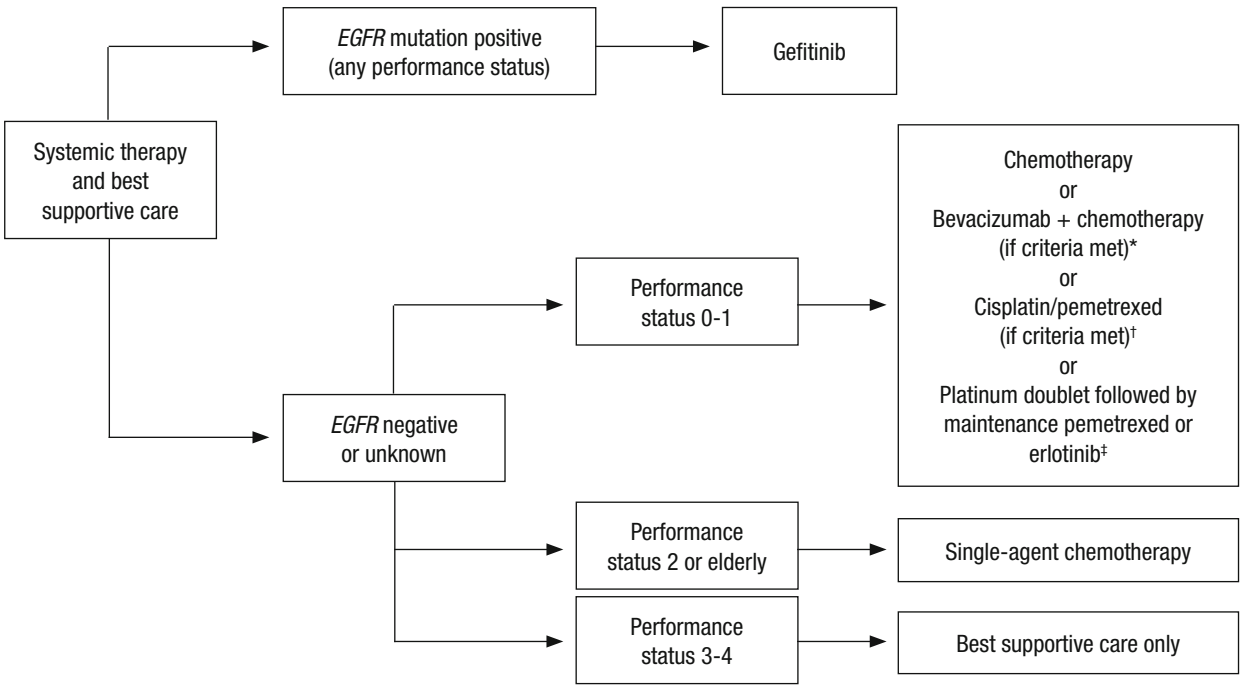
Stage III (Fig. 2)

Stage III lung cancer is defined as locoregionally advanced disease due to primary tumour extension into extrapulmonary structures (T3 or T4) or mediastinal lymph node involvement (N2 or N3) without evidence of distant metastases (M0). Although patients with a malignant pleural or pericardial effusion are considered to have stage IIIB (T4) disease in the current TNM staging system, such patients are classified as stage IV (M1a) in the newly proposed TNM staging system [4]. This change is appropriate since these patients are treated according to guidelines for stage IV NSCLC.

Stage IIIA

Three different stages are described here:

- The first one is T1–3 with no cancer found in the preoperative assessment of nodal involvement. Surgery with removal of the mediastinal nodes is recommended. If cancer is found in mediastinal lymph nodes and the surgical margins do not contain cancer, then further therapy with chemotherapy with or without radiation should be given. If the margins contain cancer, then chemotherapy followed by radiation should be given. If the original tumour could not be removed, radiation and chemotherapy are recommended.
- The second one is confirmed preoperative non-bulky mediastinal lymph node disease. The definition of bulky mediastinal lymphadenopathy varies in the literature, but a reasonable definition is lymph nodes >2 cm in short-axis diameter, as measured by CT, groupings of multiple smaller lymph nodes, or involvement of more than two lymph node stations. This distinction is primarily useful in selecting appropriate patients for surgical resection after neoadjuvant therapy. In randomised trials, survival was significantly better with induction chemotherapy plus surgical resection than with resection alone [11]. When treatment with two modalities (chemotherapy plus radiotherapy) is compared with trimodality treatment (chemotherapy plus radiotherapy plus surgery), the only benefit in several subgroups of patients has been found for the trimodality treatment (downstaging, lobectomy) [12].
- The final patient group is those with bulky N2 disease. These patients are not candidates for surgery.



*Criteria for treatment with bevacizumab + chemotherapy: non-squamous NSCLC, no clinically significant hemoptysis, no therapeutic anticoagulation and no medically uncontrolled hypertension.

†There is evidence of superior efficacy and reduced toxicity for cisplatin/pemetrexed in patients with non-squamous histology, in comparison to cisplatin/gemcitabine. Scagliotti GV, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naïve patients with advanced-stage NSCLC. J Clin Oncol 2008;26:3543-51.

‡In two recent studies, maintenance therapy with pemetrexed (only in non-squamous histology) or erlotinib increased survival in patients who has not progressed after 4 cycles of a platinum-based doublet. Ciuleanu T, et al. Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomised, double-blind, phase 3 study. Lancet 2009;374:1432-40. Cappuzzo F, et al. Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomised, placebo-controlled phase 3 study Lancet Oncol 2010; Early Online Publication, 20 May 2010.

Fig. 3 Treatment algorithm for stage IV: first-line therapy

These patients are treated with chemotherapy and radiation according to the same rules as stage IIIB (non-pleural effusion) patients.

Stage IIIB

Platinum-based chemotherapy and thoracic radiotherapy is the standard treatment for unresectable stage III patients or medically inoperable stage IIIA with good performance status and minimal weight loss.

Several approaches have been investigated including induction chemotherapy and concurrent chemoradiotherapy; both approaches have been shown to be superior to radiation therapy alone. However, in several randomised trials, concomitant chemoradiotherapy was shown to be superior to the induction chemotherapy approach [13]. It has been hypothesised that the addition of systemic dose sequential chemotherapy to concurrent chemoradiotherapy, either as induction or as consolidation chemotherapy, might further improve survival rates. However, to date, both strategies failed to further improve survival rates of concurrent chemoradiotherapy in large randomised studies [14, 15]. In addition to evaluating optimal sequencing strategies of combined modality therapy, current investigations are also focusing on the integration of novel agents, including chemotherapeutic and targeted therapies.

Stage IV (Figs. 3 and 4)

- Two-drug, platinum-based chemotherapy combined with docetaxel, gemcitabine, paclitaxel, pemetrexed or vinorelbine prolongs survival, improves quality of life and controls symptoms in patients with good performance status. Non-platinum combination chemotherapy can be considered in patients who are not fit to receive platinum agents [16].
- Timing and duration of palliative first-line treatment: chemotherapy should be initiated while the patient is in good performance status. Treatment should be stopped after no more than four cycles in patients not responding to therapy; in responding patients no more than six cycles are recommended.
- The first-line use of gefitinib may be recommended for patients with activating *EGFR* mutations. If

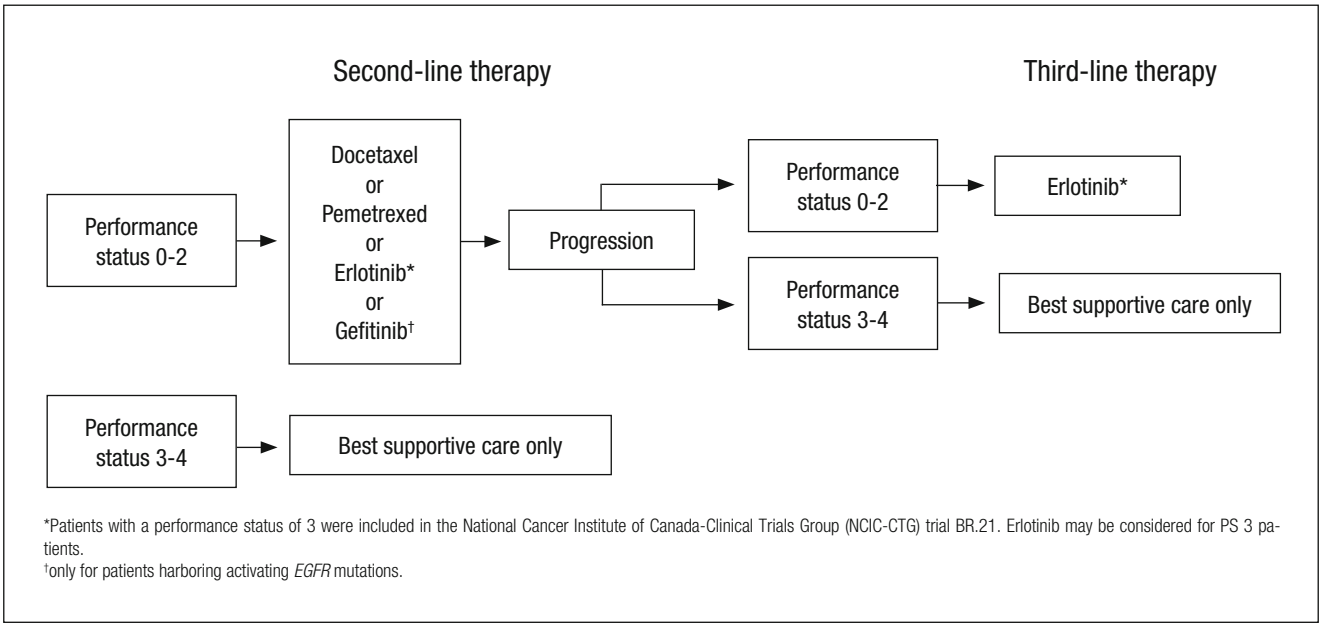


Fig. 4 Treatment algorithm for stage IV: second and third-line therapy

EGFR mutation status is negative or unknown, then cytotoxic chemotherapy is preferred [17].
- The addition of bevacizumab to chemotherapy is indicated in performance status 0–1 patients with non-squamous histology, except for patients with clinically significant haemoptysis, therapeutic anticoagulation or medically uncontrolled hypertension [18].
- There is evidence of superior efficacy and reduced toxicity for cisplatin/pemetrexed in patients with non-squamous histology, in comparison to cisplatin/gemcitabine [19].
- In two recent studies, maintenance therapy with pemetrexed (in patients with non-squamous histology who did not progress after 4 cycles of a platinum-based doublet without pemetrexed) [20] or erlotinib (in patients with any histology who achieved stable disease after 4 cycles of a platinum-based doublet) [21] increased survival.
- In elderly patients and patients with performance status 2, single-agent chemotherapy is recommended. However, some elderly patients without co-morbidity and performance status 0–1 can be treated in the same way as younger patients.
- Second-line systemic treatment with docetaxel, erlotinib, gefitinib (only for patients harbouring activating *EGFR* mutations) or pemetrexed (only in non-squamous histology) improves disease-related symptoms and survival. Erlotinib and gefitinib response rates are higher in non-smokers, women, adenocarcinomas, Asians and patients with EGFR mutations.
- Treatment with erlotinib may be recommended as third-line therapy for patients with performance status of 0–3 who have not received prior erlotinib or gefitinib [22].
- Resection of single metastases can be considered in selected cases.

Conflict of interest The authors declare that they have no conflict of interest relating to the publication of this manuscript.

Clinical Guideline Working Group on behalf of the Spanish Society of Medical Oncology (SEOM) Executive Committee 2009–2011: Emilio Alba Conejo, Juan Jesús Cruz Hernández, Álvaro Rodríguez Lescure, Javier Salvador Bofill, Pilar Garrido López, Agustí Barnadas i Molins, Joan Albanell Mestre, Pablo Borrega García, Jesús García Mata, Encarnación González Flores, Dolores Isla Casado, María Lomas Garrido

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