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CLINICAL GUIDES IN ONCOLOGY

SEOM Clinical Guidelines for the systemic treatment of early breast cancer 2013

S. Del Barco · E. Ciruelos · I. Tusquets · M. Ruiz · A. Barnadas

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Abstract The purpose of this article is to update our previous work on the treatment and follow-up in early breast cancer. In this new version we have classified a treatment by immunohistochemistry subtypes of breast cancer. Latest advances in the management of this disease have been compiled, either in the adjuvant and neoadjuvant setting or chemotherapy and hormonal treatment. This review is presented in an easy way for oncologist, fellows and for other specialties.

Keywords Breast cancer · Guidelines · Adjuvant therapy · Prognostics factors · Ending treatment · Follow-up guideline

S. Del Barco
Medical Oncology Department, Hospital Dr. Josep Trueta, Institut Català d'Oncologia (ICO), Girona, Spain

E. Ciruelos
Medical Oncology Department, Hospital Universitario, 12 de Octubre, Madrid, Spain

I. Tusquets
Medical Oncology Department, Hospital de Parc de Salut Mar, Barcelona, Spain

M. Ruiz
Medical Oncology Department, Hospital Virgen del Rocío, Sevilla, Spain

A. Barnadas (✉)
Medical Oncology Department, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain
e-mail: ABarnadasM@santpau.cat

Introduction: Systemic adjuvant therapy

Adjuvant hormonal therapy and chemotherapy improve both disease-free survival and overall survival in premenopausal and postmenopausal women. However, the decision to treat early stage breast cancer with adjuvant chemotherapy is sometimes difficult since 60–70 % of patients who receive chemotherapy would probably survive without it, while chemotherapy itself is associated with considerable morbidity and cost; moreover, some patients will suffer disease recurrence despite having received chemotherapy.

Nowadays, it is important to facilitate treatment planning with a multidisciplinary team involving radiologists, pathologists, breast surgeons, and medical and radiation oncologists, rehabilitation specialists and clinical nurses to integrate the sequence of local and systemic therapies and reduce complications.

Treatment decisions are based on several prognostic and predictive variables such as hormone receptor and HER2 status. Tumours with a high degree of ER and/or PgR expression are considered to be endocrine responsive. Patients with a total lack of ER and PgR expression in their tumours are considered endocrine non-responsive. Patients with tumours considered endocrine responsive might receive endocrine treatment alone or a combination of endocrine and chemotherapy. Patients with endocrine non-responsive tumours derive greater benefit from chemotherapy and should not receive endocrine therapy. In addition to endocrine and chemotherapy, patients with HER2 overexpression or amplification should be considered for adjuvant treatment with the trastuzumab chemotherapy combination.

For each individual, the choice of adjuvant therapy must take into account the potential benefits, possible side effects and patient preference. Multigene analyses could help

breast specialists to better estimate the risk of distant recurrences and, therefore, individualise the adjuvant strategy. Several tests are available which define prognosis (Oncotype DX, Mammaprint, PAM-50) and predictive assessment of responsiveness to chemotherapy (Oncotype DX), particularly in cases with hormone receptor positivity.

DNA microarray technologies have classified breast cancer by gene expression profile in five major subtypes: ER-positive/HER2-negative (luminal A and luminal B subtypes); ER-negative/HER2-negative (basal subtype); HER2-positive; and tumours that have characteristics similar to normal breast tissue (normal breast-like). Since it is not always feasible to obtain gene expression array information, a simplified classification defined by clinicopathological criteria is similar to, but not identical to, intrinsic subtypes different staging classifications has been proposed, on (Table 1), AJCC staging is presented.

Endocrine therapy

Adjuvant hormonal therapy is indicated in patients with early breast cancer with positive oestrogen and/or progesterone receptor expression [1]. When adjuvant chemotherapy is administered, endocrine therapy should be started at the end of chemotherapy. In addition in HER2-positive tumours, endocrine therapy can be administered concomitantly with trastuzumab but not with chemotherapy.

Table 1 AJCC staging

Stage 0
Tis, N0, M0
Stage I
T1[a], N0, M0
Stage IIA
T0, N1, M0
T1[a], N1, M0
T2, N0, M0
Stage IIB
T2, N1, M0
T3, N0, M0
Stage IIIA
T0, N2, M0
T1[a], N2, M0
T2, N2, M0
T3, N1, M0
T3, N2, M0
Stage IIIB
T4, N0, M0
T4, N1, M0
T4, N2, M0
Stage IIIC[b]
Any T, N3, M0
Stage IV
Any T, any N, M1

[a] T1 includes T1mic

[b] Stage IIIC breast cancer includes patients with any T stage who have pN3 disease. Patients with pN3a and pN3b disease are considered operable and patients with pN3c disease are considered inoperable

According to Oxford overview analyses [1, 2], after 15 years of follow-up, 5 years of tamoxifen treatment produced an 11.8 ± 1.3 % absolute reduction in breast cancer recurrence and a 9.2 ± 1.2 % reduction in breast cancer mortality in women with ER-positive tumours. The absolute improvement in breast cancer mortality associated with tamoxifen was 12.6 ± 2.0 % for women with lymph node-positive disease and 5.3 ± 0.9 % for women with node-negative disease regardless of age, adjuvant chemotherapy or tamoxifen dose. The reduction in both recurrence and mortality was twofold greater in women who had 5 years of adjuvant tamoxifen therapy compared with those who received only 1–2 years. Finally, a 49 % reduction in the rate of contralateral disease was observed among tamoxifen recipients with ER-positive or ER-unknown breast cancer after 15 years of follow-up.

The recommended duration of tamoxifen treatment is 5 years; however, the results of the ATLAS and AttoM trials suggested a benefit in reducing recurrence risk when tamoxifen is administered for 10 years; however, this benefit is only observed at the end of treatment [3].

In premenopausal patients, the combination of ovarian function suppression by LHRH analogue with tamoxifen, or tamoxifen alone (20 mg/day for 5 years) constitutes two reasonable options [2, 4]. Bilateral ovarectomy or irradiation of the ovaries leads to irreversible loss of ovarian function. Gonadotropin-releasing hormone analogues (GnRHAs) (e.g. goserelin 3.6 mg s.c. monthly) generally lead to reversible ovarian suppression. When considered in combination, they should be given for at least 2 years; however, the optimal duration of this treatment has not yet been established. When adjuvant chemotherapy is administered, the benefit of GnRHAs is not clearly demonstrated except in women under 35 years of age if ovarian function is maintained at the end of chemotherapy. The use of aromatase inhibitors in combination with ovarian function suppression is currently being tested in clinical trials; however, it might only be considered outside clinical trials when tamoxifen is contraindicated [2].

For postmenopausal patients, adjuvant hormonal treatment should include an aromatase inhibitor: anastrozole [5], letrozole [6] or exemestane [7], as initial therapy or in a sequential schedule with tamoxifen (8); any of these options can be considered appropriate (9). No differences in activity between AIs have been demonstrated in different prospective trials. The recommended duration of endocrine treatment in postmenopausal women is at least 5 years. Extended treatment with letrozole after 5 years of tamoxifen can be considered in patients with a high risk of relapse. In perimenopausal women, tamoxifen is the drug of choice for 2 or 3 years; however, when menopause is confirmed a switch from tamoxifen to IAs or extended IAs treatment at the end of

5 years of tamoxifen should be considered. The administration of AIs for 5 years produces a significant reduction in relapse risk compared to tamoxifen; however, sequential treatment with AIs and tamoxifen or vice versa obtained similar results [8].

Significant adverse events associated with tamoxifen use include venous thromboembolic events, pulmonary embolism, vaginal bleeding, vaginal discharge, ischaemic cerebrovascular events, and endometrial cancer. The long-term cardiovascular and skeletal adverse effects associated with aromatase inhibitors are an issue of concern. Women treated with aromatase inhibitors should receive vitamin D and calcium supplements, while there is no clear evidence for the use of bisphosphonates in the adjuvant setting concomitantly with aromatase inhibitors [9].

Summary: implications for clinical practice

- Tamoxifen remains the standard adjuvant endocrine treatment for premenopausal women with early hormone-responsive breast cancer.
- Ovarian suppression combined with tamoxifen would be considered in very young women after receiving adjuvant chemotherapy if ovarian function remains active.
- Aromatase inhibitors should be considered for most postmenopausal women with ER-positive breast cancer, either as initial therapy or after administration of tamoxifen for 2–5 years.
- There are no selection criteria for a specific aromatase inhibitor.
- The optimum duration of treatment with AIs is 5 or more years.
- Extended therapy with letrozole after 5 years of tamoxifen is an option for postmenopausal patients with a higher risk of recurrence.
- Monitoring for long-term adverse effects continues to pose a challenge, with special attention paid to lipid metabolism and bone health.
- A molecular assay (Oncotype DX) may help to identify patients with node-negative, ER-positive tumours at low risk for recurrence in whom tamoxifen or aromatase inhibitors alone would be adequate treatment.
- Results of on-going research will refine the ability to prescribe endocrine therapy, and integrate it more appropriately with other types of therapy.

Chemotherapy

Tumours may be divided into low or high risk of recurrence categories regarding unfavourable factors such as node involvement, age, grade, lymphovascular invasion, hormone receptor expression, HER2 amplification and proliferation. According to these the addition of chemotherapy should be considered. Furthermore, the risk of toxicity and comorbidity should be evaluated.

Recommendations should be addressed according to the following intrinsic phenotypes:

Luminal HER2 negative tumours

Luminal A In this subtype, the benefits of adjuvant chemotherapy are slight. The latest Oxford overview demonstrated the benefit of chemotherapy regardless of age, oestrogen receptor status or whether patients also receive adjuvant endocrine therapy; however, in the meta-analyses, information was lacking on tumour gene expression markers or quantitative immunohistochemistry that might help to predict risk, chemo-sensitivity, or both. Therefore, only in cases of large tumours (T3, T4) and/or N1-2 or macroscopic nodal invasion chemotherapy may be recommended [2, 3].

Luminal B HER2 negative tumours:

The presence of one or more poor prognostic factors helps us to decide whether to administer chemotherapy. Possible poor prognostic factors are: histological grade 3, T3-T4, node-positivity, progesterone receptor negativity, Ki67 $\geq$25 %, vascular or lymphatic invasion, age <35 years, a result of high-risk genetic tests (Oncotype DX, MammaPrint) [4].

Triple-negative tumours

Triple-negative pT1pN0 or pN+ represents a subgroup with a high risk of recurrence, justifying treatment with chemotherapy containing anthracyclines and taxanes [4].

Adjuvant cytotoxic chemotherapy schedule

Various chemotherapy schedules have been used. In general, the use of anthracyclines and taxanes is recommended, especially in the presence of any risk factors. In addition, no predictors of response have been identified to choose the best chemotherapy regimen.

Comparison of anthracycline-containing regimens with CMF showed a 12 % further reduction in the annual odds of recurrence ($p = 0.006$) and an 11 % further reduction in the annual odds of death ($p = 0.02$) [1, 2].

Studies using CAF/FAC (cyclophosphamide, doxorubicin, 5-fluorouracil) chemotherapy have shown that the use of full-dose chemotherapy regimens is important [1, 2, 4].

Trials comparing standard doses with dose-dense schedules with doxorubicin and paclitaxel demonstrated a 26 % reduction in hazard of recurrence ($p = 0.01$) and a 31 % reduction in the hazard of death ($p = 0.013$) in favour of the dose-dense regimen [2].

Different meta-analyses evaluated the role of taxanes in adjuvant treatment. The results showed a 17 % reduction in the risk of recurrence and 15 % in the risk of death in patients treated with anthracyclines and taxanes. The benefit was independent of the taxane type, hormone receptor status, age and nodal involvement [10]. The benefit was greater for patients with node involvement regardless of age, receptor status and HER2. In tumours without node involvement, the benefit was seen in the reduction in relapse, but not in mortality because owing to the short follow-up of the studies.

Sequential administration of anthracyclines with taxanes demonstrated a clear benefit compared to an anthracycline–cyclophosphamide combination [11]. In addition, concomitant treatment of an anthracycline with taxanes was superior when compared to an anthracycline regimen without taxanes [12]. No activity differences were observed between docetaxel and paclitaxel in the adjuvant setting, despite weekly paclitaxel being superior to 3-week paclitaxel and, 3-week docetaxel superior to weekly docetaxel.

Chemotherapy regimens widely used

- FAC/FEC: fluorouracil, doxorubicin/epirubicin, cyclophosphamide
- TAC: docetaxel, doxorubicin, cyclophosphamide
- FEC for four cycles followed by 8 weekly courses of paclitaxel (6)
- Doxorubicin or epirubicin followed by CMF
- AC with sequential paclitaxel or docetaxel
- Doxorubicin, paclitaxel, cyclophosphamide each as a single agent for four cycles given every two weeks with filgastrim support
- Docetaxel plus cyclophosphamide

HER2-positive tumours

Amplification or overexpression of human epidermal growth factor receptor 2 (HER2) is detected in 18–25 % of invasive breast cancers. It is a recognised risk of poor prognosis and predictive of targeted therapy response. Adequate assessment of HER2/neu status is critical for tailoring therapy in these patients [1, 2].

Trastuzumab is a humanised monoclonal antibody targeting the extracellular domain of the HER2 receptor.

Several prospective trials confirmed that the addition of 1 year of trastuzumab to anthracycline and/or taxane-containing adjuvant chemotherapy regimens provides substantial benefit for women with HER2-positive breast cancer, both in terms of disease recurrence and survival (approx. 50 % reduction in hazard of recurrence, and a 33 % reduction in hazard of death) [13, 14]. In those trials with trastuzumab administration, a significant increase was detected in the incidence of symptomatic cardiac dysfunction and asymptomatic decreases in LVEF. Despite close monitoring and aggressive management, combined treatment is associated with a small but real increase in the risk of myocardial dysfunction. In this way, patients must be screened for heart function before, during and after completing trastuzumab therapy, and the risks of cardiotoxicity and benefits from trastuzumab therapy must be balanced. In the BCIRG006 trial, fewer cardiac events were observed in the group of patients who received the docetaxel–carboplatin–trastuzumab combination compared to the anthracycline schedule (AC-TH) [15].

The optimum duration of trastuzumab is 1 year. Some trials suggested that concomitant administration with chemotherapy increases trastuzumab efficacy, although the risk of cardiac events could be increased.

Results of retrospective analyses of small tumours (<1 cm) without node involvement bit with HER2 overexpression pointed out their worse prognosis without trastuzumab treatment. However, none of the adjuvant pivotal trials included pT1a-b pN0, and only 12 % of patients were N0; thus, evidence of the benefit of adjuvant trastuzumab was lacking in this group. Moreover, the efficacy of adjuvant trastuzumab treatment in patients over 70 years of age has not been established.

Chemotherapy regimens in HER2+

- ACx4 (doxorubicin, cyclophosphamide) followed by paclitaxel × 12 weeks; trastuzumab × 1 year (starting with paclitaxel).
- ACx4 (doxorubicin, cyclophosphamide) followed by docetaxel × 4; trastuzumab × 1 year (starting with docetaxel).
- TCH (docetaxel, carboplatin, trastuzumab) × 6, continue trastuzumab to complete 1 year.

Special histological types of breast cancer

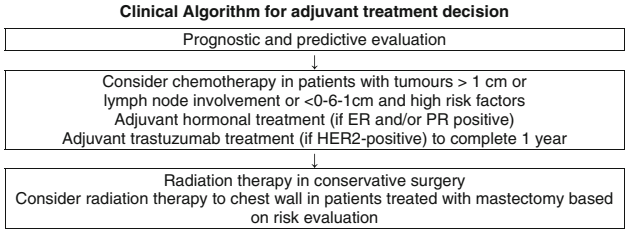
Patients with node-negative and endocrine responsive low-risk histology (tubular carcinoma, colloid, and papillary cribriform) have excellent survival with only local treatment and hormone therapy. There are no prospective data

regarding systemic adjuvant therapy on favourable histology when oestrogen receptor negativity is confirmed or in the presence of other risk factors such as tumour size or node invasion. Adenoid cystic tumour type belongs to the triple-negative subtype, but there is no recommendation for using adjuvant chemotherapy.

Medullar, metaplastic, variants of lobular carcinoma and apocrine tumours must be treated in the same way as other infiltrating ductal carcinomas based on tumour size, grade, and lymph node status.

Subtype	Type of therapy
"Luminal A"	HT alone * Consider QT if risk factor is present
"Luminal B HER2 -"	HT ±QT
"Luminal B HER2+"	QT+ Tzb + HT
"HER2+"	QT+ Tzb
"Triple negative (ductal)"	QT
"Special histological types":	
1. Endocrine responsive (HR+)	HT
2. Endocrine nonresponsive (HR-)	QT

HT: Hormonal therapy; QT: Chemotherapy (with anthracycline and taxanes or taxanes); Tzb: Trastuzumab



Neoadjuvant therapy of breast cancer

The success of preoperative chemotherapy for locally advanced and inflammatory breast cancer led to the implementation of neoadjuvant treatment in earlier disease stages as well. Neoadjuvant systemic treatment for breast cancer is a treatment option for patients with tumours not amenable to conservative surgery at diagnosis, or with some biological aspects that make them highly sensitive to neoadjuvant treatments. Its application confers the following advantages: option for conservative surgery in patients who would have had a mastectomy otherwise; predictive and prognostic information of tumour pathologic response to neoadjuvant treatment [16]; opportunity for translational trials to investigate pathological markers and their relation with response and treatment; and improved cosmetics. A unique aspect of preoperative therapy is the opportunity to monitor tumour response to therapy; nevertheless, trials have not shown improvement in outcome with treatment switch based on lack of response to initial treatment.

Disease-free and overall survival of patients treated with neoadjuvant treatment is at least equal than patients who receive adjuvant therapy.

Chemotherapy

After implementation of anthracycline-based regimens, second-generation trials focused on the addition of taxanes either in combination or sequentially, showed improved pathologic complete responses and avoided the need of further postoperative adjuvant chemotherapy. Many other chemotherapy combinations and the addition of biological agents (such as bevacizumab) have been tested, with contradictory results and no clear improvement in pCR rates over anthracycline plus taxanes regimens [17]. It is considered that accepted chemotherapy regimens for adjuvant treatment are also appropriated for neoadjuvant treatment. The optimal number of cycles is 6–8.

Adjuvant therapy

After preoperative chemotherapy, patients should receive definitive breast surgery and, when indicated as pre-chemotherapy characteristics, radiation therapy. In addition, after surgery, patients should receive adjuvant hormonal treatment if hormone receptor-positive, and trastuzumab if HER2-positive disease. To date, no trial has shown that additional chemotherapy after anthracycline and taxane-based preoperative treatment improves outcome, so it should only be considered into a clinical trial, and could be guided by residual tumour after neoadjuvant chemotherapy.

Endocrine preoperative therapy

Preoperative endocrine therapy is a treatment option for women with endocrine-sensitive tumours. With this approach, clinical responses are common, even though pathological responses are rare (<5 %). Aromatase inhibitors are superior to tamoxifen and equally effective. Outside a clinical trial, this therapy is reasonable for postmenopausal patients who are not candidates for preoperative chemotherapy either because of comorbidity or tumour biology, and should be maintained for at least 6 months. Adjuvant therapy may be considered in these cases based on response to preoperative endocrine treatment (PEPI score) [18].

HER2-positive tumours

In tumours with overexpressed or amplified HER2, adding trastuzumab to chemotherapy achieves higher pCR rates,

mostly in combination with anthracyclines and taxanes [19], although caution must be advised regarding the concomitant use of trastuzumab with anthracyclines. More recently, it has been published that new combinations of chemotherapy plus trastuzumab in combination with a second antiHER2 agent (lapatinib, pertuzumab) lead to a higher pCR rates, which might be translated into a survival benefit [20, 21].

Pathologic assessment

Any newly diagnosed patient with breast cancer suitable for systemic therapy could receive preoperative therapy without any compromise on outcome, but such approach requires careful patient selection and multidisciplinary care coordination. One important aspect of this multidisciplinary approach is pathologic assessment: adequate tissue must be obtained before preoperative systemic therapy from all suspect lesions to make histological and phenotype characterisation of the tumour. To optimise postoperative pathologic assessment, an accurate evaluation of tumour bed is essential; placement of a coil to mark the location of tumour before initiation of therapy in all patients undergoing preoperative treatment, even in those who are expected to undergo a mastectomy, can provide a most accurate pathology review.

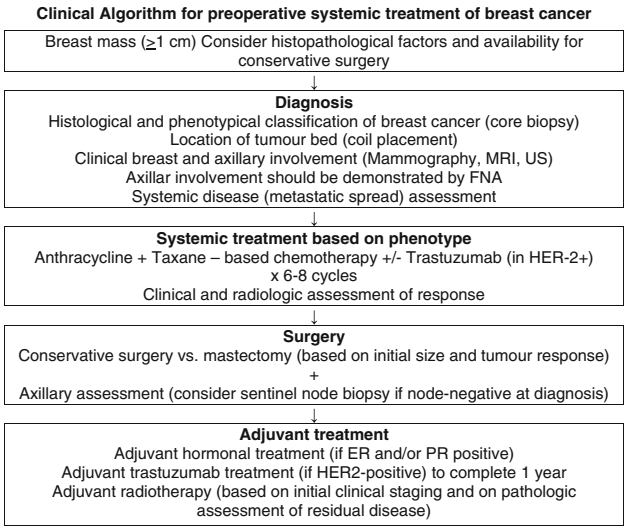
If clinically and radiologically negative axillary lymph nodes are present at diagnosis, it is possible to perform a sentinel node biopsy (SNB) before preoperative treatment or at the end of treatment when definitive surgery will be performed. If clinically or radiologically positive axillary lymph nodes are at diagnosis, the histologic assessment by FNA before preoperative systemic therapy is mandatory. Tumour involvement of axillary nodes at diagnosis might discourage the performance of sentinel node biopsy at surgery outside a clinical trial.

The achievement of pathologic complete response (pCR) has emerged as the primary endpoint of most clinical trials. It is associated with a favourable prognosis: patients who achieve pCR have lower risk of recurrence and improved survival, mostly in HER2+/RH− and triple-negative subtypes [16]. Nonetheless, the definition of pCR has varied across clinical trials: the current general definition of pCR is the absence of residual invasive cancer in both the breast and lymph nodes. The presence of residual carcinoma in situ does not affect overall survival. The presence of any amount of nodal disease after preoperative treatment predicts a poorer prognosis. Factors associated with a higher likelihood of pCR are tumour size, histology (ductal), tumour subtype (basal, HER2), hormone receptor status (negative) and grade (high).

Some recommended systemic preoperative treatment options

A number of combination and single-agent chemotherapy regimens have activity in the preoperative setting. In general, those chemotherapy regimens recommended in the adjuvant setting may be considered in the preoperative setting. If treated with endocrine therapy, an aromatase inhibitor is preferred for postmenopausal patients. In the case of HER2-positive disease, trastuzumab therapy should be added, until new combinations will be available.

AC-D (12)	Doxorubicin + cyclophosphamide × 4 followed by docetaxel × 4
AP-CMF	Doxorubicin + paclitaxel × 4 followed by CMF × 4
wP-FAC (13)	Weekly paclitaxel × 12 followed by FAC × 4
AC-wP	Doxorubicin + cyclophosphamide × 4 followed by weekly paclitaxel × 12



Surveillance

The recommendations on the follow-up of patients who have completed primary therapy with curative intent are based on a repeated consensus of experts, but there is no specific evidence based on big clinical trials designed for this purpose.

Regular physical examination and mammography are recommended for breast cancer follow-up. Physical examinations are recommended to be performed every 3–6 months for the first 3 years, every 6–12 months for

years 4 and 5, and annually thereafter. The mammographic evaluation should be performed yearly. For women who have undergone breast-conserving surgery, a post-treatment mammogram should be obtained 1 year after the initial mammogram and at least 6 months after completion of radiation therapy.

Complete blood counts, biochemistry, bone scans, chest radiographs, liver ultrasounds, pelvic ultrasounds, computed tomography scans, PET/CT, magnetic resonance imaging, and tumour markers are not recommended for routine follow-up in an asymptomatic patient.

Annual gynaecologic assessment is recommended for those women on tamoxifen adjuvant therapy. Those women on an aromatase inhibitor adjuvant programme, or who experience ovarian failure after adjuvant therapy, periodical bone health evaluations may be recommended.

Genetic counselling strategy should be recommended in those cases with high risk for hereditary breast cancer.

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

Appendix: Clinical Guideline Working Group on behalf of the Spanish Society of Medical Oncology (SEOM) Executive Committee 2011–2013

Juan Jesús Cruz, Pilar Garrido, Agustí Barnadas, Pablo Borrega, Francisco Javier Barón, Elvira del Barco, Rocio García-Carbonero, Jesús Garcia-Mata, Encarnación Gonzalez, Pilar Lianes, Antonio Llombart y Fernando Rivera.

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