Fifty Years of Progress Against Cancer – The European Organisation for Research and Treatment of Cancer Celebrates its Achievements

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Abstract

For 50 years, the European Organisation for Research and Treatment of Cancer (EORTC) has conducted and coordinated pan-European cancer clinical research and large-scale clinical trials in Europe, and many standard cancer treatments are a direct consequence of these trials. The EORTC was a pioneer in promoting multidisciplinary cancer research and is one of Europe's leading players in facilitating the passage of experimental discoveries into novel treatments for patients with cancer. In this paper, the authors present a general overview of some of the achievements that have changed medical practice in cancer treatment with particular regard to new and improved chemotherapy and multi-modal treatment, the use of imaging and diagnostics, and the development of guidelines for optimising treatment and patient quality of life.

Keywords

European Organisation for Research and Treatment of Cancer (EORTC), cancer, oncology, clinical research, translational research

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The European Organisation for Research and Treatment of Cancer (EORTC) was founded in 1962 as an international organisation under Belgian law by eminent European oncologists working in the main areas of cancer research. Originally named the Groupe Européen de Chimiothérapie Anticancéreuse (GECA), the organisation changed its name in 1968 and has been known as the EORTC ever since. Under its unifying structure, dedicated networks of researchers and clinicians have convened to conduct clinical and translational cancer research that has had a profound effect on cancer treatment not only in Europe, but worldwide. A large number of currently available standard cancer treatments are a direct consequence of this continued and collaborative effort. On these pages we present a general overview of some of its most significant achievements as it celebrates 50 years of progress against cancer.

Multimodal Cancer Treatment

The EORTC has been able to improve the standard of cancer treatment by testing more effective therapeutic strategies based on combinations of drugs and/or surgery and/or radiotherapy that are already in use and also through the development of new drugs and other innovative approaches.

Postoperative concurrent administration of high-dose cisplatin with radiotherapy was found to be more efficacious than radiotherapy alone in patients with locally advanced head and neck cancer without causing undue numbers of late complications.[1] In patients with prostate cancer at high risk of developing metastases, immediate androgen suppression with a luteinizing hormone reducing hormone agonist given during external irradiation and for three years afterwards improves 10-year disease-free survival and overall survival (OS) without increasing late cardiovascular toxicity.[2]

Completeness of surgical staging in patients with early-stage ovarian cancer was found to be associated with better outcomes, while a significant survival benefit has been shown for stage IIIC–IV ovarian cancer patients who undergo interval debulking surgery.[3–6] Neoadjuvant chemotherapy followed by interval debulking surgery is a good alternative to primary debulking surgery in these patients.

A number of EORTC trials have helped to optimise local control of breast cancer. For example, the efficacy of breast conserving surgery followed by radiotherapy was shown to be equivalent to that of mastectomy as a loco-regional treatment for operable breast cancer.[7,8] In patients with stage I/II breast cancer, an additional boost dose of radiation to the tumour bed following breast conserving surgery reduces the risk of local recurrence, especially in patients aged <50 years.[9,10] The beneficial effect of radiotherapy in reducing the overall numbers of invasive and non-invasive recurrences in the ipsilateral breast after breast-conserving surgery has also been demonstrated.[10]

Another EORTC trial showed that adjuvant chemotherapy with the combination of procarbazine, lomustine and vincristine (PCV) after radiotherapy in malignant brain tumour patients, which was once considered standard treatment, was indeed toxic and brought insufficient benefit to the patient.[11]

Brain metastases are frequent in small cell lung cancer, and two EORTC trials have led the way in the use of prophylactic cranial

irradiation with results that have made a real impact on the management of this disease and have prolonged survival.[12,13] One of these trials established the role of prophylactic cranial irradiation in advanced stage small cell lung cancer leading the way in the prevention of brain metastases, while the other trial determined the standard dose of prophylactic irradiation to be delivered to the brain.

Optimisation of Existing Cancer Treatments

Optimising treatments for patients with cancer has always been a central objective of the work of the EORTC.

In 1989, pioneering work in the field of organ preservation led to a larynx preservation strategy in patients with hypopharyngeal cancer.[14] Overall survival rates were similar for this larynx preservation strategy and conventional total laryngectomy treatment, while allowing two-thirds of patients to retain their larynx.

In successive clinical trials conducted over more than 50 years, continuous progress has been registered in the development of treatment strategies for Hodgkin's lymphoma.[15] These trials have not only improved treatment efficacy, they have also identified clinical and biological parameters that could be used to adapt the treatment strategy. Because patients enrolled in these EORTC clinical trials were followed-up on a regular basis until death, analysis of the fate of patients after each successive specific treatment has been used to develop strategies that maximise the yield of long-term responses and minimise short- and long-term toxicities in subsequent trials (see *Figure 1*).

The greatly improved outcomes brought about by the initial trials meant that later trials could aim mainly at reducing (late) treatment toxicity while maintaining excellent disease control. For example, restricting radiotherapy to the involved node was developed for patients with early stage Hodgkin's lymphoma. Moreover, the growing evidence of late effects following radiotherapy also acted as a spur to reduce doses of radiation as much as possible.[16]

The introduction of a new and significantly more efficient therapy in the treatment of childhood lymphoid malignancies was the result of an EORTC trial.[17] This trial demonstrated the superior clinical efficacy of *Escherichia coli asparaginase* over *Erwinia chrysanthemi asparaginase* in the treatment of childhood lymphoid malignancies during induction and reinduction, and this therapy is now a universal component of acute lymphoplastic leukaemia (ALL) treatment and is used in many paediatric regimens for ALL.

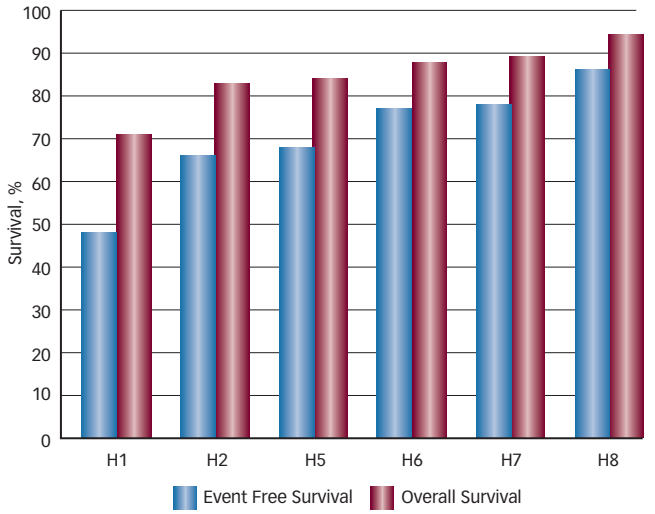
New Drug Development

The EORTC has also contributed to the development of improved drugs for treating cancer. Studies with imatinib (Glivec; Novartis) led to a dramatic improvement in overall survival in patients with metastatic gastrointestinal stromal tumours.[18]

Based on the results of an EORTC clinical trial, temozolomide (Temodar; Merck) was approved by the FDA for the treatment of adult patients with newly diagnosed glioblastoma multiforme.[19]

Carboplatin plus paclitaxel is the standard treatment for patients with non-small cell lung cancer, a treatment that was licensed following the landmark EORTC 08975 trial.[20] One EORTC study set a new standard of treatment for patients with acute myelogenous leukaemia and found that the long-term efficacy of chemotherapy is enhanced through the use of mitoxantrone or idarubicin instead of daunorubicin.[21]

Figure 1: European Organisation for Research and Treatment Hodgkins Lymphoma Trials



Survival in Six Consecutive Hodgkin Lymphoma Trials, trials H1, H2, H5, H6, H7 and H8. Source: Raemaekers J, Kluin-Nelemans H, Teodorovic I, et al., The achievements of the EORTC Lymphoma Group, Eur J Cancer, *2002;38:S107–S113.*

The US FDA approved pegylated interferon α-2b (Sylatron; Merck) for the treatment of melanoma patients with microscopic or gross nodal involvement within 84 days of definitive surgical resection including complete lymphadenectomy based on the EORTC 18991 trial.[22]

Medical management of myelodysplastic syndrome (MDS) remains a challenge, but in a clinical trial conducted by the EORTC together with the German MDS Study Group, it was shown that treatment with decitabine (Dacogen; Eisai), a drug that inhibits DNA methylation, significantly prolonged progression-free survival (PFS) in older, higher risk MDS patients.[23] A significant improvement in patient quality of life (QoL) was also observed.

Supportive Therapy

The work of the EORTC also encompasses treatments given to improve the management of complications associated with cancer treatment, such as infections and, in particular, Gram-negative sepsis and fungal infections.

A landmark study showed that infections due to Gram-negative bacilli could be managed best with a beta-lactam antibiotic and an aminoglycoside.[24] They further showed that continuing the aminoglycoside was not always necessary, thereby reducing the risk of toxicity.

In fungal infections, voriconazole (Vfend; Pfizer) was established as the drug of choice for treating invasive aspergillosis given its improved response, survival and severe side effect profile by comparison with amphotericin B. It is the benchmark against which other drugs are measured to establish an indication for treating invasive aspergillosis.[25]

Imaging

Incorporation of imaging technologies into clinical trials will enhance the delivery of appropriate treatments to patients. The EORTC has developed an Imaging Platform which will enable the development of

imaging methodologies and cancer clinical trial designs and ultimately redefine standards for high level clinical trials in cancer.

In positron emission tomography (PET) imaging, optimal image quality is essential to ensure that acquired patient images are acceptable and interpretable by any clinician in another hospital. An EORTC, EANM (European Association of Nuclear Medicine), and EARL (EANM Research Ltd.) quantitative PET Imaging accreditation program has been established to set a minimum standard for acquisition and interpretation of PET scans within EORTC clinical trials.[26]

Personalised Medicine

Genetic markers set the stage for personalised medicine and enable clear identification of patients who could benefit from a more intense treatment.

It was an EORTC trial that established the first predictive marker, the methylation status of the MGMT (O6-methylguanine–DNA methyltransferase) promoter, for helping to identify an individualised patient treatment based on the specific genetics of the brain tumour.[27] Methylation of the MGMT promoter adversely affects DNA repair and is linked to longer survival in patients with glioblastoma treated with temozolomide. The results of this trial enhanced the international recognition of European neuro-oncology research.

In women undergoing treatment for ovarian cancer, serum levels of CA125 often rise several months prior to clinical/symptomatic relapse; however, in an MRC/EORTC trial no evidence of a survival benefit or better QoL based on raised CA125 level alone was found. Routine measurement of CA125 during the follow-up of ovarian cancer patients who attain a complete response after first-line treatment is not believed to be of value, therefore.[28]

Until recently, the genes involved in the development of myelodysplastic syndrome remained largely unknown, although numerous chromosomal aberrations have been described. In a translational research study, several mutations were detected which could be indicative of early events during the evolution of this disease.[29,30]

The evaluation of response to treatment in children with ALL has been significantly advanced by studying genetic markers of this disease.[31]

Management and Assessment of Quality of Life in Cancer Clinical Trials

The EORTC has positioned itself as an international leader in methodological research in the measurement of health-related QoL in oncology, setting global standards for translation, cross cultural adaption and computer-adaptive testing at the individual patient level and as a prognostic factor.

Quality of life studies overseen by EORTC have led the way in showing how QoL data can be collected on an international basis and how the results can be used to influence clinical practice.[32,33] The results of QoL studies integrated into over 120 clinical trials have informed practice in the treatment of numerous diseases such as brain, breast, melanoma, lung and ovarian cancers.

The organisation's efforts also led to a new situation in which children with ALL are now cured with a high rate of success while avoiding undesirable acute and long-term side effects associated with irradiation of the central nervous system (CNS).[34] The deleterious side effects and long-term neurological deficits observed in survivors prompted investigators to seek other ways to reduce the risk of CNS relapse by avoiding the use of radiotherapy. In studies they found that radiotherapy could be safely spared in some groups of patients when replaced by adequate systemic and CNS-directed chemotherapy.

The key development in QoL studies over the last two decades has been the validation of EORTC QLQ-C30, a general cancer QoL questionnaire, and its incorporation into cancer clinical trials. Evidence indicates that this measurement system is now the most frequently-used QoL questionnaire in cancer clinical trials worldwide.[35]

Classifications and Guidelines

The European guidelines for the treatment of mycosis fungoides and Sezary syndrome, and the WHO–EORTC classification for cutaneous lymphomas have enabled a more uniform diagnosis, and hence a more uniform treatment, of patients with cutaneous lymphomas.[36,37] The WHO–EORTC classification represented major progress in defining this type of cancer and enabled a more reliable distinction between indolent and more aggressive types to be made as well as facilitating the selection of radiotherapy or systemic chemotherapy for first-line treatment. These guidelines and classification have been revised recently.[38,39]

The EORTC has substantially contributed to the development of definitions for diagnosis and treatment of fungal disease, and to the development of the European Conference on Infections in Leukemia (ECIL) guidelines.[40] The latter were created in order to elaborate existing guidelines for the management of infections in patients with leukaemia and those who had undergone stem cell transplants. As a result of an increasing life expectancy, the incidence of cancer cases in the older population is rising. Cancer diagnoses are 11 times more frequent in persons aged over 65 years than in younger people. The EORTC has developed specific methodology for clinical trials in the elderly[41] and has, in addition, established a standardised Elderly MinDS with the purpose of harmonising the collection of data relevant to the elderly. This should enable cross study/practice comparisons in the future.[42]

Sentinel node tumour burden has become an important stratification tool for new adjuvant studies in melanoma. Description of tumour burden using the Rotterdam Criteria and the microanatomic location of the are the most important prognostic factors for melanoma specific survival.[43] Using these guidelines, patients with minimal sentinel node tumour burden might therefore be safely spared routine completion lymph node dissection.

International Cooperation

The EORTC has played an indispensible role in actions aimed at streamlining, simplifying and harmonising the legal environment in Europe with regard to the conduct of cancer clinical trials. These efforts are in progress with the Directorate General Health and Consumers. Moreover, the organisation has a common scientific agenda with US-based co-operative groups supported by the National Cancer Institute, with the National Cancer Institute of Canada, the Australian co-operative Groups and a number of national academic groups in individual European countries. Currently 20 intergroup trials are open, and the EORTC is the leading organisation in eleven of them.

For example, EORTC trial 22981/26981 led to a global platform of four large Phase III trials in patients with brain tumours, and involved EORTC, the Radiation Therapy Oncology Group, the North Central Cancer Treatment Group and the National Cancer Institute of Canada. The MINDACT trial, for patients with breast cancer, is co-ordinated by EORTC and run under the BIG/TRANSBIG networks. It aims to provide confirmatory evidence that patients with a low recurrence risk signature (obtained using MammaPrint: Agendia; Irvine, CA) may be spared chemotherapy and its burdensome side effects without negative repercussions on survival rates. MINDACT involves sites in the Netherlands, France, Germany, Belgium, Spain, Italy, the UK, Slovenia and Switzerland, and has recruited over 6,600 patients in 111 institutions. The first results are expected in approximately three years.

Looking Forward

Over the past 50 years, EORTC research has resulted in new benchmark treatments for patients with cancer. The organisation plans to continue to further its mission to develop, conduct, coordinate and stimulate translational and clinical research in Europe to improve the management of cancer and related problems by increasing survival rates and patient QoL.

Further therapeutic advances will most likely arise from a clinical trial platform that incorporates strong translational research, imaging, biobanking, quality assurance in radiotherapy and in surgery, and research studies aimed at understanding the biology of the disease. This will lead to the development of specific treatments for a fragmented disease that was previously seen as a single entity.

This effort will involve the formation of partnerships with a variety of stakeholders, certainly with other academic groups and learned societies, but also patient organisations, cancer leagues, regulatory agencies and the pharmaceutical industry. In this way, EORTC will ensure that it continues to provide improved treatments for patients with cancer. ■

1. Bernier J, Domenge C, Ozsahin M, et al., European Organization for Research and Treatment of Cancer Trial 22931. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer, *N Engl J Med*, 2004;350:1945–52.
2. Bolla M, Van Tienhoven G, Warde P, et al., External irradiation with or without long-term androgen suppression for prostate cancer with high metastatic risk: 10-year results of an EORTC randomised study, *Lancet Oncol*, 2010;11:1066–73.
3. Trimbos JB, Vergote I, Bolis G, et al., Impact of adjuvant chemotherapy and surgical staging in early-stage ovarian carcinoma. European Organisation for Research and Treatment of Cancer. Adjuvant chemotherapy in ovarian neoplasm trial, *J Natl Cancer Inst,* 2003;95(2):113–24.
4. Trimbos JB, Parmar M, Guthrie D, et al., International Collaborative Ovarian Neoplasm trial 1 and Adjuvant ChemoTherapy In Ovarian Neoplasm trial: two parallel randomized phase III trials of adjuvant chemotherapy in patients with early-stage ovarian carcinoma, *J Natl Cancer Inst*, 2003;95:105–12.
5. Colombo N, Guthrie D, Parmar M, et al.,International Collaborative Ovarian Neoplasm trial 1: a randomized trial of adjuvant chemotherapy in women with early-stage ovarian cancer, *J Natl Cancer Inst*, 2003;95:125–32.
6. Trimbos B, Timmers P, et al., Surgical staging and treatment of early ovarian cancer: long-term analysis from a randomized trial, *J Natl Cancer Inst*, 2010;102:982–7.
7. Van Dongen JA, Voogd AC, Fentiman IS, et al., Long-term results of a randomized trial comparing breast-conserving therapy with mastectomy: European Organization for Research and Treatment of Cancer 10801 trial, *J Natl Cancer Inst,* 2000;92:1143–50.
9. Bartelink H, Horiot JC, Poortmans PM, et al., Impact of a higher radiation dose on local control and survival in breast-conserving therapy of early breast cancer: 10-year results of the randomized boost versus no boost EORTC 22881-10882 trial, *J Clin Oncol*, 2007;25:3259–65.
9. Bartelink H, Horiot JC, Poortmans PM, et al., Recurrence rates after treatment of breast cancer with standard radiotherapy with or without additional radiation, *N Engl J Med*, 2001;345:1378–87.
10. Julien JP, Bijker N, Fentiman IS, et al., Radiotherapy in breast-conserving treatment for ductal carcinoma *in situ*: first results of the EORTC randomised phase III trial 10853, *Lancet*, 2000;355:528–33.
11. Van den Bent MJ, Carpentier AF, Brandes AA, et al., Adjuvant procarbazine, lomustine, and vincristine improves progression-free survival but not overall survival in newly diagnosed anaplastic oligodendrogliomas and oligoastrocytomas: a randomized European Organisation for Research and Treatment of Cancer phase III trial, *J Clin Oncol*, 2006;24:2715–22.
12. Slotman B, Faivre-Finn C, Kramer G, et al., Prophylactic cranial irradiation in extensive small-cell lung cancer, *N Engl J Med*, 2007;357:664–72.
13. Le Pechoux C, Dunant A, Senan S, et al., Standard-dose versus higher-dose prophylactic cranial irradiation (PCI) in patients with limited-stage small-cell lung cancer in complete remission after chemotherapy and thoracic radiotherapy (PCI 99-01, EORTC 22003-08004, RTOG 0212, and IFCT 99-01): a randomised clinical trial, *Lancet Oncol*, 2009;10:467–74.
14. Lefebvre J-L, Chevalier D, Luboinski B, et al., Larynx preservation in hypopharynx and lateral epilarynx cancer: Preliminary results of EORTC randomized phase III trial 24891, *J Natl Cancer Inst*, 1996;88:890–9.
15. Raemaekersa J, Kluin-Nelemans H, Teodorovic I, et al. on behalf of the EORTC Lymphoma Group, The achievements of the EORTC Lymphoma Group, *Eur J Cancer*, 2002;38:S107–13.
16. Eghbali H, Raemaekers J, Carde P, The EORTC strategy in the treatment of Hodgkin's lymphoma, *Eur J Haematol*, 2005;66:135–40.
17. Duval M, Suciu S, Ferster A, et al. for the European Organisation for Research and Treatment of Cancer-Children's Leukemia Group, Comparison of E. coli-asparaginase with Erwinia-asparaginase in the treatment of childhood lymphoid malignancies, results of an EORTC-CLG Phase III randomized trial, *Blood*, 2002;99:2734–9.
18. Verweij J, Casali PG, Zalcberg J, et al., Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomised trial, *Lancet*, 2004;364:1127–34.
19. Stupp R, Mason WP, van den Bent MJ, et al., Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma, *N Engl J Med*, 2005;352:987–96.
20. Smit EF, van Meerbeeck J, Lianes P, et al., Three-arm randomized study of two cisplatin-based regimens and paclitaxel plus gemcitabine in advanced non-small-cell lung cancer: a phase III trial of the European Organization for Research and Treatment of Cancer Lung Cancer Group--EORTC 08975, *J Clin Oncol*, 2003;21:3909–17.
21. Mandelli F, Vignetti M, Suciu S, et al., Daunorubicin versus mitoxantrone versus idarubicin as induction and consolidation chemotherapy for adults with acute myeloid leukemia: The EORTC and GIMEMA groups study AML-10, *J Clin Oncol*, 2009;27:5397–403.
22. Eggermont AMM, Suciu S, Santinami M, et al. for the EORTC Melanoma Group. Adjuvant therapy with pegylated interferon alfa-2b versus observation alone in resected stage III melanoma: Final results of EORTC 18991, a randomised phase III trial, *Lancet*, 2008;372:117–26.
23. Lübbert M, Suciu S, Baila L, et al., Low-dose decitabine versus best supportive care in elderly patients with intermediate- or high-risk myelodysplastic syndrome (MDS) ineligible for intensive chemotherapy: final results of the randomized Phase III study of the European Organisation for Research and Treatment of Cancer Leukemia Group and the German MDS Study Group, *J Clin Oncol*, Published online before print April 11, 2011, doi:10.1200/JCO.2010.30.9245
24. Schimpff SC, Gaya H, Klastersky J, et al., Three antibiotic regimens in the treatment of infection in febrile granulocytopenic patients. The EORTC International Antimicrobial Therapy Project Group, *J Infect Dis*, 1978;137:14–29.
25. Herbrecht R, Denning DW, Patterson TF et al., Voriconazole versus amphotericin b for primary therapy of invasive aspergillosis, *N Engl J Med*, 2002:347:408–15.
26. Boellaard R, O'Doherty MJ, Weber WA, et al., FDG PET and PET/CT: EANM procedure guidelines for tumour PET imaging: version 1.0, *Eur J Nucl Med Mol Imaging*, 2010;37:181–200.
27. Hegi ME, Diserens AC, Gorlia T, et al., MGMT gene silencing and benefit from temozolomide in glioblastoma, *N Engl J Med*, 2005;352:997–1003.
28. Rustin GJ, van der Burg MEL, Griffin CL, et al., Early versus delayed treatment of relapsed ovarian cancer (MRC OV05/EORTC 55955): a randomised trial, *Lancet*, 2010;376:1155–63.
29. Langemeijer SMC, Kuiper RP, Berends M, et al., Acquired mutations in TET2 are common in myelodysplastic syndromes, *Nature Genetics*, 2009;41:838–43.
30. Nikoloski GN, Langemeijer SMC, Kuiper RP, et al., Somatic mutations of the histone methyltransferase EZH2 gene in myelodysplastic syndromes, *Nature Genetics*, 2010;42:665–7.
31. Cavé H, Van Der Werff Ten Bosch J, Suciu S, et al. for the EORTC-Childhood Leukemia Cooperative Group, Clinical significance of minimal residual disease in childhood acute lymphoblastic leukemia, *N Engl J Med*, 1998;339:591–8.
32. Bottomley A, Aaronson NK, International perspective on health-related quality-of-life research in cancer clinical trials: The European Organisation for Research and Treatment of Cancer experience, *J Clin Oncol*, 2007;25:5082–6.
33. Bottomley A, Quinten C, Coens C, et al., Patient reported outcomes: Assessment and current perspectives of the guidelines of the Food and Drug Administration and the reflection paper of the European Medicine Agency, *Eur J Cancer*, 2009;45:347–53.
34. Vilmer E, Suciu S, Ferster A, et al., Long-term results of three randomized trials (58831, 58832, 58881) in childhood acute lymphoblastic leukemia: a CLCG-EORTC report. Children Leukemia Cooperative Group, *Leukemia*, 2000;14:2257–66.
35. Aaronson NK, Ahmedzai S, Bergman B, et al., The EORTC QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology, *J Natl Cancer Inst*, 1993;85:365–76.
36. Willemze R, Jaffe ES, Burg G, et al., WHO-EORTC classification for cutaneous lymphomas, *Blood*, 2005;105:3768–85.
37. Trautinger F, Knobler R, Willemze R, et al., EORTC consensus recommendations for the treatment of mycosis fungoides/Sezary syndrome, *Eur J Cancer*, 2006;42:1014–30.
38. Olsen EA, Whittaker S, Kim YH, et al., Clinical end points and response criteria in mycosis fungoides and Sézary syndrome: a consensus statement of the International Society for Cutaneous Lymphomas, the United States Cutaneous Lymphoma Consortium, and the Cutaneous Lymphoma Task Force of the European Organisation for Research and Treatment of Cancer, *J Clin Oncol*, 2011;29:2598–607.
39. Olsen E, Vonderheid E, Pimpinelli N, et al., Revisions to the staging and classification of mycosis fungoides and Sézary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the cutaneous lymphoma task force of the European Organization of Research and Treatment of Cancer (EORTC), *Blood*, 2007;110:1713–22.
40. Ascioglu S, Rex JH, de Pauw B, et al., Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: an international consensus, *Clin Infect Dis*, 2002;34:7–14.
41. Pallis AG, Fortpied C, Wedding U, et al., EORTC elderly task force position paper: approach to the older cancer patient, *Eur J Cancer*, 2010;46:1502–13.
42. Pallis AG, Ring A, Fortpeid C, et al., EORTC workshop on clinical trial methodology in older individuals with a diagnosis of solid tumors, *Ann Oncol*, 2011;22:1922–6.
43. Van der Ploeg APT, van Akkooi ACJ, Rutkowski P, et al., Prognosis in patients with sentinel node–positive melanoma is accurately defined by the combined rotterdam tumor load and dewar topography criteria, *J Clin Oncol*, 2011;29:2206–14.