Staging of cancer

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Cancer is a generic term for a group of over 100 diseases that can affect any anatomic site. It is a leading cause of death with approximately 8 million people expected to die of cancer this year worldwide. Assessment of the burden of cancer is required to develop a comprehensive cancer control plan. Cancer surveillance requires the knowledge of the type of cancer, which is classified by site according to the international classification of diseases and the histological classification. In addition, the anatomic extent of cancer is recorded according to the UICC/AJCC TNM Classification of Malignant Tumours. These essential elements permit tracking of the incidence and mortality from cancer and assessment of the impact of cancer control measures including prevention, screening, early detection and treatment. Assessment of disease extent, that is, staging of cancer, is therefore one of the fundamental activities in oncology. Knowledge of the anatomic extent of disease is essential to characterise cancer prior to treatment [1,2].

The key pieces of information needed for the management and reporting of results in patients with cancer, site of origin, histologic type, and anatomic extent of disease are classified and coded according to the International Classification of Diseases for Oncology (ICD-10 and ICD-O) for the primary site and the World Health Organization Histological Classification of Tumours [3] that provides definitions, nomenclature and classification of tumour types. Assessment of the anatomic extent of disease at diagnosis – or cancer stage – is classified by the TNM staging classification [2,4,5].

The TNM classification is the worldwide benchmark for reporting the extent of malignant disease, and is both the main determinant influencing the choice of treatment and the most important prognostic factor in predicting the outcome of patients with cancer [1,6]. The definition of cancer staging provided in Wikipedia®, a multilingual, Web-based, free-content encyclopedia project is [7]: *"... The stage of a cancer is a descriptor (usually numbers I to IV) of how much the cancer has spread. The stage often takes into account the size of a tumor, how deep it has penetrated, whether it has invaded adjacent organs, if and how many lymph nodes it has metastasized to, and whether it has spread to distant organs. Staging of cancer is important because the stage at diagnosis is the most powerful predictor of survival, and treatments are often changed based on the stage ..."*

The TNM classification [8,9] provides for the description of the primary tumour (T), spread to the regional lymph nodes (N), and distant metastasis (M). The combination of the T, N, and M categories results in grouping into stages: I, II, III, or IV. This system for classifying anatomic extent of cancer has existed for more than 50 years [4,10]. With time and sequential editions, the TNM classification has evolved to accommodate new knowledge and management developments [1,6,11,12]. The current (sixth) edition [8] was published in 2002. The formal development of a systematic classification of the anatomic extent of disease using the TNM system is attributed to Pierre Denoix and the International Union Against Cancer (UICC) through its TNM Project [10]. In 1959, the American Joint Committee on Cancer (AJCC) began publishing separate definitions of the TNM categories for various sites, using the histopathologic extent of disease as the basis for classification. In 1987, under the leadership of Beahrs, Baker, and Hutter from AJCC and Sobin and Hermanek from the UICC, both TNM classifications [8,13] were unified, and at present are identical.

The aims of staging originally described by Pierre Denoix and adopted by the UICC TNM Project are shown in Table 1. These aims make the TNM classification clinically vital, but at the same time bring potential limitations. For example, testis cancer patients with different disease stage may have similar excellent prognosis but those with stage I may be cured

Table 1
Aims of cancer staging

- To aid the clinician in planning treatment
- To give some indication of prognosis
- To assist in evaluating the results of treatment
- To facilitate the exchange of information between treatment centres
- To contribute to continuing investigations of human malignancies

with orchiectomy alone, while those with stage II disease require additional treatment. In kidney cancer, patients may have different prognosis (stage I versus stage II) but require the same treatment with surgery. Since knowledge about prognostic factors and the availability of effective cancer therapy continually expand [11,14,15], the TNM classification needs to adapt and change in order to remain clinically relevant [1,12,16].

Staging and prognosis

Clinical practice in cancer is based on prevention, diagnosis, and treatment. All are based on the prediction of possible outcomes, the prognosis. Appraisal of a patient's prognosis is part of everyday practice and studies of prognostic factors are integral to cancer research [11,17,18]. In addition to the site of origin (e.g. lung or breast), histology (e.g. adenocarcinoma or squamous cell carcinoma) and stage [11], definition of the outcome in cancer depends on a number of additional variables considered under the umbrella of prognostic factors. These factors can account for the heterogeneity associated with the expected course and outcome of a disease. Knowledge of prognostic factors helps the understanding of the natural history of cancer. The management of cancer patients requires us to make predictions and decisions for individuals. The challenge of prognostication is to link the individual patient to the collective population of patients with the same disease characteristics and treated in the same manner that form the basis of prognostication [11]. Whilst the TNM staging classification is the standard system for recording anatomic disease extent, there is no standard system for classifying prognostic factors. However, numerous prognostic indexes [19] and nomograms [20] are used in the clinic.

The prognosis in cancer is commonly equated with tumour characteristics including histologic type, grade, depth of invasion, or the presence of lymph-node metastasis. Pathology and stage account for most variations in cancer outcome. However, factors not directly related to the tumour also affect the course of disease and the outcome. Three broad groups encompass factors those related to disease or *tumour*, to the *host* or patient, and to the *environment* in which the patient is found. In the management of cancer patients, determination of prognosis is required repeatedly at multiple situations along the course of the disease. Factors related to the presence of the tumour include histology, stage, or factors reflecting tumour biology (Table 2). While histology forms the basis of tumour classification today, progress in molecular medicine has led to redefinition of many cancers according to molecular and genetic tumour characteristics. Molecular and genetic criteria are now accepted in acute leukaemia, lymphoma, synovial sarcoma, Ewings tumour, etc and are being considered in other cancers. Most tumour-related molecular factors such as gene expression patterns deal with disease characterisation. Details of tumour pathology are crucial to the determination of prognosis in cancer. The histologic type has traditionally defined the individual cancers, but grade, pattern of growth, immunophenotype, also reflect the fundamental type of disease under consideration. Tumour multi-focality, the presence of lymphatic or vascular invasion, and infiltration patterns may relate both to type of disease

Table 2
Examples of tumour related prognostic factors

Pathology
Molecular tumour characteristics; gene expression patterns
Morphologic classification – e.g. adenocarcinoma, squamous
Histologic grade
Growth pattern – e.g. papillary versus solid, cribriform versus tubular versus solid
Pattern of invasion – e.g. perineural, small vessel invasion
Anatomic tumour extent
TNM categories
Tumour bulk
Single versus multifocal tumour
Number of sites of involvement
Tumour markers – e.g. PSA, AFP, CEA
Tumour biology
Tumour markers – e.g. her2neu, CD20
Proliferation indices – e.g. S-phase fraction, MiB-1
Molecular markers – p53, rb, Bcl2
Symptoms – related to the presence of tumour

Table 3
Examples of host related prognostic factors

Demographics
Age
Race
Gender
Level of education
Socioeconomic status
Religion
Co-morbidity
Inherited immune deficiency
von Recklinghausen disease etc.
Coexistent illness, e.g. inflammatory bowel disease
Weight
Cardiac status
Acquired immune deficiency
Infection
Mental health
Performance status
Compliance
Social reaction to illness
Influence of habits, drugs, alcohol, smoking, etc.
Belief in alternative therapies

and the extent [21,22]. Hormone receptors, expression of proliferation-related factors and molecular tumour characteristics relate more to the type of cancer rather than the disease extent [23,24].

The TNM categories and stage groupings describe anatomic disease extent. Tumour bulk, number of involved sites, involvement of specific organs, levels of tumour markers like PSA, CA 125, CEA, and AFP strongly correlate with tumour bulk and anatomic disease extent [25,26].

Factors in the host (patient) not directly related to malignancy may significantly impact the final outcome (Table 3). These include demographics including age [27], gender [28] and racial origin [29]), co-morbidity and coexistent illnesses [30], especially those affecting the immune status [31], performance status related to co-morbid illness, and factors that relate to the host mental state, attitude and compliance [32] with therapy. A history of prior cancer and treatment of that cancer also places survivors at risk for future events.

Numerous factors external to the patient may affect the prognosis (Table 4). Three broad categories may be defined including those related to expertise including the choice of a specific treatment plan and caregiver skill, those related to the health care system including access to health insurance, cancer care and organised screening programmes, calibre of medical record keeping, internet access, etc. Finally there are factors related to a societal focus such as socio-economic [33] and nutritional status, and quality of care, with impact on outcome.

Taxonomy of prognostic factors

In the English language, prediction, forecasting, and prognosis all indicate the probability of future events. In the medical literature, however, the use of the terms such as predictive, prognostic, and risk are being freely substituted for each other without much thought about consistent and accurate definitions. In the epidemiology literature, a *risk factor* is defined as 'a clearly defined occurrence or characteristic that has been associated with the increased rate of a subsequently occurring disease'; thus it is limited to patients who currently do not have a disease. In contrast, a *prognostic factor* refers to a probability of future event in patients who do currently have a disease.

Henderson and colleagues [34] and others defined the term 'predictive' as 'prognosis for a measurable response' of overt tumour reduction following a treatment intervention and uses the term 'predictive factor' as distinct from 'prognostic' factor. The authors considered a prognostic factor in the narrow context of a probability of cure or prolongation of survival. An example of a prognostic factor that is not a predictive factor is the number of involved axillary lymph nodes in breast cancer [22]. A high number of lymph nodes is associated with inferior survival, but the number of involved lymph nodes has little impact on response to treatment. In contrast, a factor that is both predictive and prognostic is the oestrogen receptor status in breast cancer that predicts for response to hormonal therapy, but also prognosticates for a better survival. Another example, HER-2-neu status, is both a predictive and prognostic factor [35]. It is debatable whether such a distinction, which focuses on a single intermediate outcome (a measurable response to cytotoxic treatment) instead of defined endpoint relating to overall prognosis (e.g. local tumour control, survival), should be embraced.

In addition to the distinction between the terms prediction and prognosis, a further issue requiring clarification is distinguishing cancer staging and prognostic classifications. Factors that indicate anatomic disease extent and bulk should be reflected in staging classification. Those that indicate the *biology* of disease including histopathology, genetic and molecular factors should be part of the WHO Classification of Tumour Pathology and ultimately part of the ICD

Table 4
Examples of environment related prognostic factors

	Related to		
	Treatment	Education	Quality
Physician	Choice of physician or specialty quality of diagnosis accuracy of staging Choice of treatment Expertise of physician – 'narrow experts' Timeliness of treatment Ageism	Ignorance of medical profession Access to internet Knowledge, education of the patient Participation in clinical trials Participation in continuing education	Quality of treatment Skill of the physician Treatment verification
Health Care System	Access to appropriate diagnostic methods Access to care distance waiting lists monopoly control of access to care Availability of publicly funded screening programmes	Continuing medical education Lack of audit of local results Access to internet Development of practice guidelines Dissemination of new knowledge	Quality of equipment Quality management in treatment facility Maintenance of health records Availability of universal health insurance Quality of diagnostic services Implementation of screening programmes Promotion of error free environment
Society	Preference for unconventional therapies Socioeconomic status Distance from cancer centre Insurance status Access to transportation, car, etc. Ageism	Literacy Access to information	Access to affordable health insurance Nutritional status of the population

classification. Together, all the factors that help to define the prognosis including tumour, host, and environment factors are included in prognostic indexes and nomograms.

Clinical-relevance-based classification

To consider the relevance of prognostic factors in clinical practice, prognostic factors in this book are placed in three distinct categories: *essential, additional*, and *new and promising factors*. *Essential* factors are those that are fundamental to decisions about the goals and choice of treatment, and include details regarding the selection of treatment modality and specific interventions. Inherent in this definition is that knowledge of these essential factors are required to meet a published clinical practice guideline [36]. The *additional* factors allow finer prognostication, but are not an absolute requirement for the treatment related decision-making process. Their role is to communicate prognosis, but they do not in themselves influence treatment choice. *New and promising factors* are those that shed new light about the biology of disease, or the prognosis for patients but for which currently there is, at best, incomplete evidence of an independent effect on outcome or prognosis [11,37]. The main factor required to make treatment decision is the type of cancer defined by histology or molecular tumour characteristics. The second most important group of essential factors reflects the anatomic disease extent. Many other essential factors have been identified including pathology, tumour biology, tumour-related symptoms, patient age, performance status, newer imaging methods [38], and tumour markers [39] are also integral to the decision making process in the choice of a treatment modality. In addition to the essential factors, there are numerous variables that help to define the outcome more precisely, but are not required for general decisions about treatment. These include more detailed histologic features, host-related factors, including co-morbid conditions and vital organ function, which influence the suitability for surgery, chemotherapy, or radiotherapy. Environment-related factors, such as the choice of an inferior treatment plan, poor quality diagnostic tests or treatments themselves have the potential to compromise the outcome. Management in a specialised unit in several tumour sites for example in breast, colorectal cancer and paediatric brain tumours [40], has resulted in improved survival in population-based studies. The immense and rapid expansion of molecular biology has provided an abundance of opportunities to study new biologic prognostic factors [14,41] which hold promise for future applications. Molecular factors such as epidermal growth factor receptor (EGFR) status [42] may be used to predict response to a treatment modality, or they may present a target for therapy such as imatinib in gastrointestinal stromal tumours [43]. Alternatively they may assist in treatment stratification such as MGMT status which predicts for chemotherapy and radiotherapy responsiveness in Glioblastoma multiforme [44]. Another category includes factors that predict for the presence of occult distant metastases. See Table 3 for examples of new and promising prognostic factors.

Table 5
Applications of cancer staging

Patient care
Select appropriate diagnostic tests
Select an appropriate treatment plan
Predict the outcome for individual patient
Establish informed consent
Assess the outcome of therapeutic intervention
Select appropriate follow-up monitoring
Provide patient and caregiver education
Research
Improve the efficiency of research design and data analysis
Enhance the confidence of prediction
Demarcate phenomena for scientific exploration
Design future studies
Identify subgroups with poor outcomes for experimental therapy
Identify groups with excellent outcomes for simplified therapy
Identify candidates for organ preservation trials
Cancer control programs
Plan resource requirements
Assess the impact of screening programmes
Assess access to a timely diagnosis
Introduce and monitor clinical-practice guidelines
Monitor results
Provide public education
Explain variation in the observed outcomes

There are numerous applications of the information collected in cancer staging. They include but are not limited to the impact on direct patient care. Table 5 provides examples of the broad range of application of cancer staging encompassing patient care to research and cancer control.

The UICC TNM Prognostic Factors Project

The mission of the UICC (International Union against Cancer) TNM Prognostic Factors (TNM PF) Project

is to provide and maintain a worldwide clinically relevant staging (TNM classification) and prognostic factor [45] classification for cancer, and to promote global consensus on these classifications. The TNM PF Project utilises a variety of strategies to meet these goals. These strategies include development and expansion of the UICC TNM Global Advisory Group initiative, and the TNM review process. The Global Advisory Group initiative aims to increase global representation, create and network national cancer staging committees worldwide [46]. Its objectives are to enhance international collaboration in securing TNM staging classification as a standard for describing anatomic disease extent, to facilitate open-ended participation in international cancer staging efforts, and to build capacity in both cancer staging and prognostic factor classifications.

Like any other classification, to be generally applicable, TNM classification requires consensus and acceptance by oncology opinion leaders and practitioners. In recent years, opinion alone is insufficient as evidence to guide practice. The introduction of evidence based medicine has led to significant changes in the process of developing clinical practice guidelines [36] and similarly, evidence is required to develop or change staging classification [47,48]. Expert review of a systematic search of published literature and review of evidence from clinical trials and large clinical databases [49,50] with mature outcomes is required.

The TNM classification was modified over the years to improve its prognostic ability and applicability to changing methods of treatment [6]. Historically, changes to the TNM classification were derived from a decision-making process based on expert opinion from several national TNM committees and from the individual membership of the UICC TNM Committee [46]. However, complex changes have emerged that have made it increasingly difficult to use the previous procedures to review and assess proposals for changes and to make appropriate, evidence based decisions.

Over the past few years, the UICC TNM Prognostic Factor Project Committee has revised the process for amending the TNM classification [1]. The new process expands the methods and tools for evaluating the proposed changes to the classification and emphasises the continuous monitoring, improvement, and adaptation of the TNM. Assessing the quality of the evidence is the main focus of the new process. This process requires a multidisciplinary approach and the inclusion of all involved in the treatment of patients with cancer and in the reporting of outcome data [51]. Two key activities were introduced; firstly, a process for considering proposals to revise TNM or to create a new classification, and secondly, the continuous literature review that identifies opportunities for improving the system. In 2002, the UICC introduced a structured process for initiating changes to the TNM classification [1]. This process contained four key elements: (1) the development of clear and unambiguous criteria for changes to TNM; (2) the establishment of a well defined process for the annual review of relevant literature (the 'Literature Watch'); (3) the formation of disease site-specific Panels of Experts and (4) the acquisition of global expertise and participation in the TNM review process [46]. The key goals of the annual Literature Watch process include: (1) identifying new opportunities to improve the TNM classification, (2) reviewing criticism of the existing TNM classification, (3) identifying gaps in the TNM classification - specifically in areas where no classification exists, (4) reviewing proposals for amendments to the TNM system that should be reviewed by the TNM Prognostic Factors Task Force, and (5) gathering evidence for the use of the TNM classification in both clinical and outcome research. Multidisciplinary 'Panels of Experts' in major disease sites act in an advisory capacity to assist in judging the current status, or any new development, in the cancer staging classification. Over the 5 years since establishment of the Annual Literature Watch, this process has developed a standardised methodology for identifying published articles with a specific focus in cancer staging. Moreover, it helps ensure that relevant, important, and contemporary issues for practitioners in the field are given their due consideration and addressed by a systematic and thorough methodology.

Summary

To be relevant to clinical practice, cancer staging must predict the outcomes, or be used to select treatment methods. It is likely that with progress in treatment, and improved outcomes, cancer stage and other prognostic factors will lead to treatment that is increasingly individually tailored to each patient. Knowledge of anatomic disease extent is also required to minimise the deleterious impact of treatment. Improved diagnostic methods, and especially more accurate characterisation of microscopic disease extent could help define a more homogeneous grouping of patients with similar disease characteristics and tumour-related prognostic factors, for a specified disease. Knowledge of genetic or molecular factors will lead to improved classification of cancer and

provide new therapeutic targets and may further add to the improved prediction of outcome and greater individualisation of therapeutic interventions. However, grouping of patients into similar categories according to disease extent prior to treatment will continue to be required to assess the impact of new technology in patient assessment and new therapies on outcome.

Conflict of interest statement

None declared.

References

1 Gospodarowicz MK, Miller D, Groome PA, Greene FL, Logan PA, Sobin LH. The process for continuous improvement of the TNM classification. *Cancer* 2004, **100**(1), 1–5.
2 Brierley J. The evolving TNM cancer staging system: an essential component of cancer care. *CMAJ* 2006, **174**(2), 155–156.
3 World Health Organization. International statistical classification of diseases and health related problems, 10th revision (ICD-10). Second ed. Geneva; 2005.
4 Sobin LH. TNM: principles, history, and relation to other prognostic factors. *Cancer* 2001, **91**(Suppl 8), 1589–1592.
5 Greene FL, Sobin LH. The TNM system: our language for cancer care. *J Surg Oncol* 2002, **80**(3), 119–120.
6 Sobin LH. TNM: evolution and relation to other prognostic factors. *Semin Surg Oncol* 2003, **21**(1), 3–7.
7 Wikipedia. http://en.wikipedia.org/wiki/Cancer_Staging. Access date May 26, 2007.
8 UICC – International Union against Cancer. *TNM Classification of malignant tumors*. Sixth ed. New Jersey, John Wiley & Sons, 2002.
9 UICC – International Union against Cancer. TNM – Online. In: Gospodarowicz MK, Henson,D.E.,Hutter,R.V.P.,O'Sullivan, B.,Sobin,L.H.,Wittekind,Ch., editors. First ed. New York: Wiley-Liss; 2006.
10 Gospodarowicz M, Benedet L, Hutter RV, Fleming I, Henson DE, Sobin LH. History and international developments in cancer staging. *Cancer Prev Control* 1998, **2**(6), 262–268.
11 Gospodarowicz MK, O'Sullivan B.,Koh, E-S. Prognostic factors:Principles and applications. In: Gospodarowicz MK, O'Sullivan B.,Sobin, L.H., eds. *Prognostic factors in cancer*. Third ed. New York, Wiley-Liss, 2006, 23–38.
12 Sobin LH. TNM, sixth edition: new developments in general concepts and rules. *Semin Surg Oncol* 2003, **21**(1), 19–22.
13 *AJCC cancer staging manual*. Sixth ed. New York, Springer, 2002.
14 Liu GG, Zhou, W, Wang, Z, Mcleod, H.L. Incorporating molecular oncology into prognosis. In: Gospodarowicz MK, O'Sullivan B., Sobin LH, eds. *Prognostic factors in cancer*. Third ed. New York, Wiley-Liss, 2006, 79–94.
15 Glare P. Prognostic factors in terminal care. In: Gospodarowicz MK, O'Sullivan B., Sobin LH, eds. *Prognostic factors in cancer*. Third ed. New York, Wiley-Liss, 2006, 63–78.
16 Hermanek P, Sobin LH, Wittekind C. How to improve the present TNM staging system. *Cancer* 1999, **86**(11), 2189–2191.
17 Gospodarowicz M, Mackillop W, O'Sullivan B, *et al.* Prognostic factors in clinical decision making: the future. *Cancer* 2001, **91**(Suppl 8),1688–1695.
18 Mackillop WJ. The Importance of prognosis in cancer medicine. In: Gospodarowicz MK, O'Sullivan B, Sobin LH, eds. *Prognostic factors in cancer*. Third ed. New York, Wiley-Liss, 2006, 3–22.
19 Perea G, Altes A, Montoto S, *et al.* Prognostic indexes in follicular lymphoma: a comparison of different prognostic systems. *Ann Oncol* 2005, **16**(9), 1508–1513.
20 Stephenson AJ, Kattan MW. Nomograms for prostate cancer. *BJU Int* 2006, **98**(1), 39–46.
21 Baak JP, van Diest PJ, Voorhorst FJ, *et al.* Prospective multicenter validation of the independent prognostic value of the mitotic activity index in lymph node-negative breast cancer patients younger than 55 years. *J Clin Oncol* 2005, **23**(25), 5993–6001.
22 Truong PT, Yong CM, Abnousi F, *et al.* Lymphovascular invasion is associated with reduced locoregional control and survival in women with node-negative breast cancer treated with mastectomy and systemic therapy. *J Am Coll Surg* 2005, **200**(6), 912–921.
23 DiGiovanna MP, Stern DF, Edgerton SM, Whalen SG, Moore 2nd D, Thor AD. Relationship of epidermal growth factor receptor expression to ErbB-2 signaling activity and prognosis in breast cancer patients. *J Clin Oncol* 2005, **23**(6), 1152–1160.
24 Buscarini M, Quek ML, Gill P, Xia G, Quinn DI, Stein JP. Molecular prognostic factors in bladder cancer. *BJU Int* 2005, **95**(6), 739–742.
25 D'Amico AV, Renshaw AA, Sussman B, Chen MH. Pretreatment PSA velocity and risk of death from prostate cancer following external beam radiation therapy. *Jama* 2005, **294**(4), 440–447.
26 Gorog D, Regoly-Merei J, Paku S, Kopper L, Nagy P. Alpha-fetoprotein expression is a potential prognostic marker in hepatocellular carcinoma. *World J Gastroenterol* 2005, **11**(32), 5015–5018.
27 Hurria A, Leung D, Trainor K, Borgen P, Norton L, Hudis C. Factors influencing treatment patterns of breast cancer patients age 75 and older. *Crit Rev Oncol Hematol* 2003, **46**(2), 121–126.
28 Batevik R, Grong K, Segadal L, Stangeland L. The female gender has a positive effect on survival independent of background life expectancy following surgical resection of primary non-small cell lung cancer: a study of absolute and relative survival over 15 years. *Lung Cancer* 2005, **47**(2), 173–181.
29 Chlebowski RT, Chen Z, Anderson GL, *et al.* Ethnicity and breast cancer: factors influencing differences in incidence and outcome. *J Natl Cancer Inst* 2005, **97**(6), 439–448.
30 Maas HA, Kruitwagen RF, Lemmens VE, Goey SH, Janssen-Heijnen ML. The influence of age and co-morbidity on treatment and prognosis of ovarian cancer: a population-based study. *Gynecol Oncol* 2005, **97**(1), 104–109.
31 Straus DJ. Prognostic factors in the treatment of human immunodeficiency virus-associated non-Hodgkin's lymphoma. *Recent Results Cancer Res* 2002, **159**, 143–148.
32 Verkooijen HM, Fioretta GM, Rapiti E, *et al.* Patients' refusal of surgery strongly impairs breast cancer survival. *Ann Surg* 2005, **242**(2), 276–280.
33 Mackillop WJ, Zhang-Salomons J, Groome PA, Paszat L, Holowaty E. Socioeconomic status and cancer survival in Ontario. *J Clin Oncol* 1997, **15**(4), 1680–1689.
34 Henderson IC, Patek AJ. The relationship between prognostic and predictive factors in the management of breast cancer. *Breast Cancer Res Treat* 1998, **52**(1–3), 261–288.

35 Smith I, Procter M, Gelber RD, *et al.* 2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial. *Lancet* 2007, **369**(9555), 29–36.
36 Woolf SH. Evidence-based medicine and practice guidelines: an overview. *Cancer Control* 2000, **7**(4), 362–367.
37 Specht L. Prognostic factors in Hodgkin lymphoma. In: Gospodarowicz MK, O'Sullivan B, Sobin LH, eds. *Prognostic factors in cancer*. Third ed. New York, Wiley-Liss, 2006, 281–284.
38 Borst GR, Belderbos JS, Boellaard R, *et al.* Standardised FDG uptake: a prognostic factor for inoperable non-small cell lung cancer. *Eur J Cancer* 2005, **41**(11), 1533–1541.
39 Lam JS, Shvarts O, Leppert JT, Figlin RA, Belldegrun AS. Renal cell carcinoma 2005: new frontiers in staging, prognostication and targeted molecular therapy. *J Urol* 2005, **173**(6), 1853–1862.
40 Smith ER, Butler WE, Barker 2nd FG. Craniotomy for resection of pediatric brain tumors in the United States, 1988 to 2000: effects of provider caseloads and progressive centralization and specialization of care. *Neurosurgery* 2004, **54**(3), 553–563, discussion 563–565.
41 Russo A, Bazan V, Iacopetta B, Kerr D, Soussi T, Gebbia N. The TP53 colorectal cancer international collaborative study on the prognostic and predictive significance of p53 mutation: influence of tumor site, type of mutation, and adjuvant treatment. *J Clin Oncol* 2005, **23**(30), 7518–7528.
42 Bentzen SM, Atasoy BM, Daley FM, *et al.* Epidermal growth factor receptor expression in pretreatment biopsies from head and neck squamous cell carcinoma as a predictive factor for a benefit from accelerated radiation therapy in a randomized controlled trial. *J Clin Oncol* 2005, **23**(24), 5560–5567.
43 Van Glabbeke M, Verweij J, Casali PG, *et al.* Initial and late resistance to imatinib in advanced gastrointestinal stromal tumors are predicted by different prognostic factors: a European Organisation for Research and Treatment of Cancer-Italian Sarcoma Group-Australasian Gastrointestinal Trials Group study. *J Clin Oncol* 2005, **23**(24), 5795–5804.
44 Hegi ME, Diserens AC, Gorlia T, *et al.* MGMT gene silencing and benefit from temozolomide in glioblastoma. *N Engl J Med* 2005, **352**(10), 997–1003.
45 Gospodarowicz M, O'Sullivan B. Prognostic factors in cancer. *Semin Surg Oncol* 2003, **21**(1), 13–18.
46 Sobin LH, Greene FL. Global TNM Advisory Group. *Cancer* 2004, **100**(5), 1106.
47 Mackillop WJ, O'Sullivan B, Gospodarowicz M. The role of cancer staging in evidence-based medicine. *Cancer Prev Control* 1998, **2**(6), 269–277.
48 Altman DG. Studies investigating prognostic factors: Conduct and evaluation. In: Gospodarowicz MK, O'Sullivan B, Sobin LH, eds. *Prognostic factors in cancer*. Third ed. New York, Wiley-Liss, 2006, 39–54.
49 Perng RP, Chen CY, Chang GC, *et al.* Revisit of 1997 TNM staging system – survival analysis of 1112 lung cancer patients in Taiwan. *Jpn J Clin Oncol* 2007, **37**(1), 9–15.
50 Balch CM, Soong SJ, Atkins MB, *et al.* An evidence-based staging system for cutaneous melanoma. *CA Cancer J Clin* 2004, **54**(3), 131–149, quiz 182–184.
51 Singletary SE, Greene FL. Revision of breast cancer staging: the 6th edition of the TNM Classification. *Semin Surg Oncol* 2003, **21**(1), 53–59.