Design issues in head and neck clinical trials: a statistician's perspective

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The purpose of this article is to present some of the challenges the trial statistician meets when designing a clinical trial of the head and neck cancer. In recent years, the field of head and neck cancer has been facing some exciting evolutions, such as the arrival of newly targeted therapies and findings of disease causality and prognosis. These evolutions are accompanied by challenges in trial methodology that continue even today, and will most likely grow in importance in the future. This article focuses essentially on the design of phase III trials and discusses three major topics: should the trial be designed for a broad or a targeted population? Is there a concern for lack of equipoise and if so, how will it affect the trial results? What are the key elements that need to be taken into consideration when choosing, defining, and measuring the primary endpoint? *Anti-Cancer Drugs* 22:682–687 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

The design of clinical trials in oncology, in general, and in the head and neck cancer, in particular, poses a number of challenges to the trial statistician.

Evidence-based medicine (EBM) provides scientific grounds for establishing new standards of care and treatment guidelines. The most common definition of EBM is taken from Dr David Sackett who was a pioneer in EBM. EBM is 'the conscientious, explicit and judicious use of current best evidence in making decisions about the care of an individual patient. It means integrating individual clinical expertise with the best available external clinical evidence from systematic research' [1]. 'Statistics is central to evidence-based medicine', said Sally Morton, the president of the American Statistical Association in 2009. Indeed, statistics provide a set of tools to design clinical trials and interpret the study results.

In designing the trial, the mission of the trial statistician is to make a proposal that will provide estimates of treatment effect with minimal bias and maximal precision, while taking into account the characteristics of the disease, therapy options, study objectives, feasibility of the trial, and ethics, costs, and regulatory considerations.

The head and neck cancer trial statistician shares, with other therapeutic areas, the same design issues when planning a clinical trial: definition of the objectives; specification of the patient population; randomization and stratification; definition of endpoints and unbiased collection of those; and computation of the sample size.

The purpose of this article is to review a number of design issues the statistician struggles with, taking into account the specificity of the head and neck cancer disease and the constantly evolving biological and therapeutic knowledge. This article focuses essentially on the design of phase III trials and discusses three major topics: should the trial be designed for a broad or a targeted population? Is there a concern for lack of equipoise and if so, how will it affect the trial results? What are the key elements to take into consideration when choosing, defining, and measuring the primary endpoint?

Broad population versus targeted population

Head and neck cancers are a heterogeneous group of diseases. European Society for Medical Oncology clinical recommendations for diagnosis, treatment, and follow-up make a split between squamous cell carcinoma of the head and neck (90% of the head and neck malignancies) and nasopharyngeal cancers [2]. Although some nasopharyngeal cancers are biologically similar to the common squamous cell carcinoma, 'poorly differentiated' nasopharyngeal carcinoma is distinct in its epidemiology, biology, clinical behavior, and treatment, and is treated as a separate disease by many experts (*http://en.wikipedia.org/wiki/Head_and_neck_cancer*). The US National Cancer Institute's gateway for information about the head and neck cancer makes a further split by providing information about the treatment separately for the following subtypes: hypopharyngeal cancer, laryngeal cancer, lip and oral cavity cancer, metastatic squamous neck cancer with occult primary treatment, nasopharyngeal cancer, oropharyngeal cancer, paranasal sinus and nasal cavity cancer, and salivary gland cancer. These subtypes correspond primarily to the site at which cancer arises (the primary site) (*http://www.cancer.gov/cancertopics/types/head-and-neck/*).

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The design of a clinical trial proceeds, first, with the specification of the goal of the trial and this is intrinsically linked to the specification of the targeted population. Eligibility criteria can be defined either narrowly or broadly, depending on a priori considerations about homogeneity of treatment effect across subtypes. Each of the two options has different consequences in terms of homogeneity/heterogeneity of the sample population, accrual rate and duration of the trial, and generalizability of the study results [3]. In addition, when planning the sample size and trial duration, we need to make assumptions about the outcome in the control arm and the magnitude of the treatment effect and these estimates are strongly dependent on the population under study.

In one approach to designing cancer trials, the eligibility criteria first comprises the specification of the tumor site(s) and of the clinical stage, based on the universal TNM classification system. This may be called the classical way.

With regard to the tumor sites, several sites may be included, and in fact most often are, but this requires that the magnitude of the treatment effect, usually expressed in terms of hazard ratio for a phase III trial, is similar across these sites. In addition, as there are differences in survival prognosis across tumor sites [4], the randomization of patients needs to be stratified by site to balance treatment arms across sites. Moreover, prognostication and planning of the trial will depend on the estimates of the outcome in the control arm and these can be obtained from earlier trials, provided the targeted sites are the same and the 'mix' is the same.

Such a trial is designed for a specific clinical stage (early, advanced, recurrent, or metastatic). TNM staging is constantly evolving and the American Joint Committee on Cancer (AJCC)/International Union Against Cancer system is now in its seventh edition (*http://www.cancerstaging.org/*). Staging is currently based on anatomical considerations and improvements of diagnostic imaging and in particular the increasing use of PET scans may lead to stage migration in head and neck squamous cell carcinoma [5]. We need to take this evolution into account while using historical data to design new trials.

Historically, the concept of resectability was of great importance as surgery was the primary treatment option for resectable cases. Radiotherapy was reserved for unresectable cases or as a postoperative treatment. Nowadays, radiotherapy in combination with or without chemotherapy or targeted therapies is offered as an option in resectable cases, as an attempt to spare the severe morbidity caused by surgery. It is also remarkable to see that the terms 'resectable' and 'unresectable' have been replaced with 'moderately advanced' and 'very advanced' in the seventh edition of the American Joint Committee on Cancerstaging manual (*http://www.cancerstaging.org/staging/changes2010.pdf*). For a clinical trial designed to test the effect of a therapeutic approach based on radiotherapy, chemotherapy, and/or targeted therapy, the choice between designing a trial for unresectable patients only, or for both resectable and unresectable poses specific issues. Although restricting the trial to unresectable patients is inconvenient in terms of accrual and generalizability of the study results, the extension to resectable patients opens the door to the use of salvage surgery thus inducing a potential bias in the assessment of the treatment effect. Some investigators advocate the inclusion of either resectable or unresectable patients in the trial, but not both, to define the most beneficial treatment option in each of the two settings [6].

In the future, patient selection criteria may be mainly by gene mutation or marker based. Indeed, some investigators advocate the inclusion of biological characteristics in the staging system to refine the prognostic value of staging [7]. Whether these biological factors have an added prognostic or predictive value beyond known clinical prognostic factors needs to be carefully evaluated [8]. Molecular studies in the past 10 years have shown that human papillomavirus (HPV), a sexually transmitted infection, is an etiologic factor for a subset of oropharyngeal cancer. These studies indicate that patients with HPV mediated cancer have better prognosis and clinical outcomes than those without, with the conclusion that HPV positive disease is a 'distinct disease entity' that needs a distinct therapeutic approach [8,9]. Current investigations are now being done to further understand the pathogenesis of the head and neck cancer and the relevance of tumor markers such as the p53 tumor suppressor gene, cyclin D1, Bcl-xL and Bcl-2, STAT1 and STAT3, ERCC1, thymidylate synthase, GST-π, β-tublin-II, and HER neu [10,11]. Advances in this research area will open new classifications of the disease. From a study design point of view, distinct disease calls for different study objectives, as for example, it is now obvious that a single study cannot include all oropharynx cancers irrespective of the HPV status, the first reason being a very large difference in prognosis. We also wonder whether classification of patients based on gene mutation or marker will not ultimately prevail over classifications based on tumor sites, such as designing clinical trials on patients selected according to their HPV status irrespective of the disease site.

Feasibility of the trial

Although randomized controlled trials are the gold standard in terms of trial design, they are not a sufficient condition for a rigorous evaluation of new therapeutic interventions. 'A key ethical precept is that a randomized controlled trial should be done only if the physicians and the patients are uncertain about the relative effects of the new and standard treatments to be compared' [12]. This notion of equipoise was already discussed by Freedman, back in the 1980s, stating that 'equipoise is an ethically necessary condition in all cases of clinical research' [13].

The incidence of head and neck cancer is relatively low as compared with some other cancer types. The recent update of GLOBOCAN (*http://globocan.iarc.fr/*) shows that head and neck cancer accounts for 5% of all cancers worldwide in 2008 while lung cancer, breast cancer, and colorectal cancer account for 13, 11, and 10% respectively. Patient accrual is thus a challenge necessitating multicenter and collaborative trials to recruit sufficient patients. In addition, the head and neck cancer trials involve clinicians from different specialties: medical oncologists, radiation oncologists, surgeons, etc. Together, the acceptability and feasibility of a proposed trial is a challenge as different preferences can be indicated by these different groups. An Australian study aimed to measure equipoise among surgeons and oncologists (mostly radiation oncologists, but also some medical oncologists) with regard to six different hypothetical trials in head and neck cancer. The study showed considerably preferential differences between surgeons and oncologists [14], stating that the same trial can be considered as not acceptable by some specialties while well supported by others, and this has an inevitable impact on the feasibility of the trial.

Blinding

'Blinding or masking is intended to limit the occurrence of conscious and unconscious bias in the conduct and interpretation of a clinical trial' (*http://www.ich.org/LOB/media/MEDIA485.pdf*). In cancer clinical trials blinding is rarely possible, especially when surgery or radiotherapy are part of the treatment or because of the toxicity related to one of the treatments. This means that the risk of bias is higher in these trials and in particular the risk benefit assessment is more open to subjective interpretation.

Bias

Clinician or patient preference for one of the treatment arms results in a barrier in terms of recruitment. Moreover it results in selective enrollment of patients: the distribution of the enrolled patients differs from the target population thus affecting the generalizability of the study findings. Katz *et al.* advocate an assessment of the extent, nature, and effect of selective enrollment, something that is neither routinely done nor requested. We thus encourage the collection of the reasons for noninclusion of patients in the trial, although we recognize that such a collection will also inevitably suffer from some bias.

If the selection of patients is made with respect to factors associated with efficacy, trial results will be distorted and lead to inaccurate conclusions [15]. Clinician or patient preference may induce an unbalanced compliance to the study protocol, making the interpretation of the study data even more difficult.

As statisticians, and because of the open labeled nature of the majority of cancer trials, we are strongly concerned about these potential biases.

Risk benefit assessment

In terms of trial design, the principle of uncertainty is to be ensured by appropriate choice of treatment arms including the control intervention and documentation of their benefits and risks in the study protocol. The assessment of risk, and toxicity in particular, suffers from a lack of accuracy. Indeed, variability between reporting physicians and cultural differences induces heterogeneity in the collection of toxicity data. Here as well, bias in the assessment of toxicity between treatment arms may arise because of the open labeled nature of cancer trials. A minimal safeguard to ensure unbiased comparison is, therefore, to stratify the randomization for investigational site.

Of note, 'equipoise must be maintained throughout the trial duration and this requires an ongoing knowledge of clinical research that may impact the trial meaning' [16]. In some cases, evolving knowledge necessitates a redesign, such as adding, deleting, or modifying a treatment arm, during the course of the trial.

With the emergence of targeted treatments, which has potentially fewer toxic effects, guaranteeing equipoise represents a new challenge, as the a priori perceived balance of benefits and risk may be in favor of targeted therapy as compared with classical cytotoxic chemotherapy [17,18]. Head-to-head trials comparing targeted therapies may be necessary to reach clinical equipoise [19].

Choice of endpoint

The gold standard primary endpoint for phase III cancer trials is overall survival as this represents the ultimate goal in terms of benefit for the patient. It has the advantage of being precisely measured but it usually requires long and/or large studies compared with a trial based on an earlier endpoint. Indeed when survival is long, an adequately powered trial will either take long to observe the required number of events or will require a large number of patients. In addition, overall survival may be affected by the relative effectiveness of subsequent treatments, possibly including crossover between treatment arms. Because of these drawbacks, alternative time-to-event endpoints are often proposed as primary endpoint and overall survival is kept as a secondary endpoint. The choice of the primary endpoint will be influenced by the type of treatment and the type of trial [3], but there are usually several possible alternatives.

A review of 40 trials in advanced head and neck cancer patients treated with radiation-based therapy showed substantial heterogeneity in the selection and in the definition of the time-to-event endpoints [20]. The authors report that the most commonly used primary endpoints are overall survival (35% of the trials) and locoregional control (35% of the trials). However, locoregional control can have different definitions depending on which events are counted as failures. Some

of the reviewed studies included distant metastasis, salvage surgery, elective neck dissection, second cancer, and/or death as an event. In addition to overall survival and disease specific survival, the authors recommend the use of locoregional control and progression-free survival (PFS) in trials of radiation-based therapy for locally advanced head and neck cancer, with a definition of these endpoints similar to the ones used in the Radiation Therapy Oncology Group 0522 trial. The definition of locoregional control includes locoregional progression and recurrence, death because of the malignancy, and some cases of neck dissection and salvage surgery as failures; the definition of PFS includes distant metastasis and death because of any cause as failures.

To draw conclusions on treatment effect using endpoints that can be measured more quickly than overall survival and hence shorten trial duration and cost, two endpoints were evaluated as potential surrogate endpoints for overall survival to assess the treatment effect of chemoradiotherapy in trials of locally advanced head and neck squamous cell carcinoma: event-free survival (defined as time from randomization to the first of locoregional, distant recurrence, or death) and duration of locoregional control [21]. The investigators show that event-free survival could be used as a surrogate. It is to be noted, however, that these results cannot be extended to other types of treatment, such as targeted agents, as the mode of action differs and therefore the correlation between treatment effects on the surrogate endpoint and overall survival may be different.

For adjuvant (postoperative) trials, endpoints such as disease-free survival, disease-free intervals are usually proposed.

For organ-preservation trials, a recent publication recommends that the primary endpoint should combine the assessment of survival and organ functions [22]. For larynx preservation trials, the end point 'laryngo-esophageal dysfunction-free survival' is defined when the following events are counted as failures: death, local relapse, total or partial laryngectomy, tracheotomy at 2 years or later, or feeding tube at 2 years or later.

In the recurrent and/or metastatic setting, where for most patients the duration of survival will be short, overall survival is the preferred primary endpoint [23]. But if the goal of treatment is to relieve symptoms or side effects of treatment, quality of life endpoints are also relevant.

A common issue across these different settings when selecting the appropriate time-to-event endpoint is to define which events are counted as failure, that is, which events compose this (usually composite) endpoint. The events that are not counted as failures will need to be treated appropriately using right hand censoring or the competing risk approach. For example, a patient lost to follow-up or having reached the end of follow-up before having failed will be censored. A competing risk analysis should ideally be carried out in the presence of events, which are not a part of the composite time-to-endpoint but are related to it to some extent. One example is a trial for which the event of interest is a local failure; distant metastases and secondary cancers diagnosed before locoregional relapse and death in the absence of locoregional progression are not considered failures for this endpoint, but are considered to be competing risks in the analysis of this endpoint. This method has been used for the analysis of secondary endpoints in some head and neck cancer trials, such as one trial in the postoperative setting where death from other causes was considered as a competing risk in the analysis of local or regional relapse, distant metastasis and secondary primary tumors [24].

It is also important to evaluate whether these events can be potentially observed in each of the arms evaluated in the trial. An example that was already mentioned above is when salvage surgery is more likely to be proposed in one of the treatment arms. The choice whether salvage surgery is counted as a failure in the definition of the primary endpoint or ignored will have an impact on the estimated time-to-event in this arm with a potentially subsequent bias in one or the other direction when comparing the treatment arms. Censoring at the time of salvage surgery is not an option as this gives rise to informative censoring. Actually (and alarmingly) there is no best solution. This example shows the difficulties the trial statistician faces when trying to reconcile best clinical practice and unbiased assessment of treatment effect.

Another issue is the impact of assessment schedule on the estimated time-to-progression. Disease progression (whether local, regional, or distant) is usually assessed through radiological evaluations made at protocol specified intervals of time. The estimated time-to-disease progression is therefore influenced by the length of these intervals. It is crucial that the scheduled intervals are the same between the treatment arms to not induce a bias in the treatment effect. However, this obvious statement may be difficult to be put into practice, especially when treatments evaluated are of different duration, or when one arm consists of a sequential treatment and the other arm consists of concomitant treatment (e.g. if we wish to compare induction computed tomography followed by radiation therapy with concomitant chemoradiation). The estimates of the treatment effect will be biased if the length of intervals differs significantly between the arms. Moreover, the comparison of treatment effects across trials is misled if the length of intervals differ significantly from trial to trial [25,26].

In the field of head and neck cancer, where several treatment options are possible (chemotherapy, biotherapy, radiotherapy, surgery), and where these are being combined in different ways (concomitant, sequential)

with different possible doses or schedules, only if one factor is changed between treatment arms we can attribute the observed treatment difference in the endpoint to this factor. However, often, treatment arms within the same trial differ by several factors, and it is thus not possible to learn from the trial which factor or which combination of factors have influenced the difference in outcome and this is regrettable from a methodological perspective.

Conclusion

In recent years, the field of head and neck cancer has been facing some exciting evolutions, such as the arrival of new targeted therapies and findings of disease causality and prognosis. These evolutions are accompanied by challenges in trial methodology that continue today, and will most likely grow in importance in the future.

Novel drugs are incorporated into already complex treatment strategies (involving sequences of multimodality treatments that condition on outcomes of the preceding treatment), making the study endpoints difficult to evaluate without bias. Trials comparing such strategies have evaluation schemes that are (differently) affected by the timing of radiotherapy and surgery, making an unbiased assessment and comparison of PFS and similar endpoints difficult. In situations where this assessment meets too many problematic scenarios, PFS may not be a feasible primary endpoint.

In addition, the temptation to examine several investigational questions within a limited number of randomized arms leads to trials where causality is difficult to evaluate at the end of the trial. If more than one factor is changed between treatment arms (e.g. where complex combined treatment approaches are fine-tuned), it becomes difficult to interpret the true cause of observed effects. Simple trials provide stronger proof.

At the same time, it is essential to obtain unbiased evaluation of the feasibility and toxicity of such regimens, to enable correct benefit–risk assessment of novel approaches. This is especially challenging in the habitual open-labeled setting of oncology trials. Those involved in the design of clinical trials need to be aware that although the area of efficacy comparison is well developed and great efforts go into the consistent collection of efficacy data, there can be serious heterogeneity in safety collection among trials, investigational sites, cultures, and investigational drugs (open label trials). Methodological steps such as stratified randomization can provide a partial answer to such concerns. Still, reporting of adverse effects that is more homogeneous and extended in time remains a goal for oncology clinical trials, including the head and neck cancer.

Efforts on translational research are essential in modern oncology research. As in other cancer types, the additional science obtained may divide what once looked like a relatively homogeneous disease area. It will be essential to define the new core areas of research into the disease, because every clinical trial necessarily and unavoidably pools together a large number of individual cases. Therein lies the challenge of combining trial feasibility (numbers) and scientific validity (homogeneity) to produce a valuable clinical trial. Defining these new core areas may imply that, with appropriate stratification, some of the classical separation lines are reconsidered.

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References

1 Sackett DL, Rosenberg WM, Gray JA, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. *BMJ* 1996; **312**:71–72.
2 Grégoire V, Lefebvre J-L, Licitra L, Felip E, On behalf of the EHNS-ESMO-ESTRO Guidelines Working Group. Squamous cell carcinoma of the head and neck: EHNS-ESMO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010; **21** (**Suppl 5**):v184–v186.
3 Sylvester R, Van Glabbeke M, Collette L, Suciu S, Baron B, Legrand C, *et al.* Statistical methodology of phase III cancer clinical trials: advances and future perspectives. *Eur J Cancer* 2002; **38** (**Suppl 4**):S162–S168.
4 Zigon G, Berrino F, Gatta G, Sánchez MJ, Van Dijk B, Van Eycken E, *et al.*; the EUROCARE Working Group. Prognoses for head and neck cancers in Europe diagnosed in 1995-1999: a population-based study. *Ann Oncol* 2010. [Epub ahead of print]
5 Misono S, Rue T, Rajendran J, Davis GE. Effects of upstaging from PET scan on survival in head and neck squamous cell carcinoma. *Head Neck* 2010. [Epub ahead of print]
6 Yun HJ, Bogaerts J, Awada A, Lacombe D. Clinical trial design limitations in head and neck squamous cell carcinomas. *Curr Opin Oncol* 2007; **19**:210–215.
7 Takes RP, Rinaldo A, Silver CE, Piccirillo JF, Haigentz M Jr, Suárez C, *et al.* Future of the TNM classification and staging system in head and neck cancer. *Head Neck* 2010. [Epub ahead of print]
8 Brandwein-Gensler M, Smith RV. Prognostic indicators in head and neck oncology including the new 7th edition of the AJCC staging system. *Head Neck Pathol* 2010; **4**:53–61. [Epub 6 February 2010]
9 Vidal L, Gillison ML. Human papillomavirus in HNSCC: recognition of a distinct disease type. *Hematol Oncol Clin North Am* 2008; **22**: 1125–1142. vii.
10 Cojocariu OM, Huguet F, Lefevre M, Périé S. Prognosis and predictive factors in head-and-neck cancers. *Bull Cancer* 2009; **96**:369–378.
11 Cullen KJ, Schumaker L, Nikitakis N, Goloubeva O, Tan M, Sarlis NJ, *et al.* Beta-tubulin-II expression strongly predicts outcome in patients receiving induction chemotherapy for locally advanced squamous carcinoma of the head and neck: a companion analysis of the TAX 324 trial. *J Clin Oncol* 2009; **27**:6222–6228. [Epub 16 November 2009].
12 Djulbegovic B, Kumar A, Soares HP, Hozo I, Bepler G, Clarke M, *et al.* Treatment success in cancer: new cancer treatment successes identified in phase 3 randomized controlled trials conducted by the National Cancer Institute-sponsored cooperative oncology groups, 1955 to 2006. *Arch Intern Med* 2008; **168**:632–642.
13 Freedman B. Equipoise and the ethics of clinical research. *N Engl J Med* 1987; **317**:141–145.
14 Young JM, O'Brien C, Harrison JD, Solomon MJ. Clinical trials in head and neck oncology: an evaluation of clinicians' willingness to participate. *Head Neck* 2006; **28**:235–243.
15 Katz JN, Wright J, Levy BA, Baron JA, Losina E. Departures from community equipoise may lead to incorrect inference in randomized trials. *J Clin Epidemiol* 2010. [Epub ahead of print].
16 Schroen AT, Petroni GR, Wang H, Gray R, Wang XF, Cronin W, *et al.* Preliminary evaluation of factors associated with premature trial closure and feasibility of accrual benchmarks in phase III oncology trials. *Clin Trials* 2010; **7**:312–321. [Epub 1 July 2010].

17 Pritchard-Jones K, Dixon-Woods M, Naafs-Wilstra M, Valsecchi MG. Improving recruitment to clinical trials for cancer in childhood. *Lancet Oncol* 2008; **9**:392–399.
18 Meropol NJ. A renewed call for equipoise. *J Clin Oncol* 2007; **25**: 3392–3394.
19 Pal SK, Figlin RA. Targeted therapies for renal cell carcinoma: understanding their impact on survival. *Target Oncol* 2010; **5**:131–138. [Epub 15 July 2010]
20 Le Tourneau C, Michiels S, Gan HK, Siu LL. Reporting of time-to-event end points and tracking of failures in randomized trials of radiotherapy with or without any concomitant anticancer agent for locally advanced head and neck cancer. *J Clin Oncol* 2009; **27**:5965–5971. [Epub 5 October 2009]
21 Michiels S, Le Maître A, Buyse M, Burzykowski T, Maillard E, Bogaerts J, *et al.*; MARCH and MACH-NC Collaborative Groups. Surrogate endpoints for overall survival in locally advanced head and neck cancer: meta-analyses of individual patient data. *Lancet Oncol* 2009; **10**:341–350. [Epub 24 February 2009]
22 Lefebvre JL, Ang KK; Larynx Preservation Consensus Panel. Larynx preservation clinical trial design: key issues and recommendations-a consensus panel summary. *Int J Radiat Oncol Biol Phys* 2009; **73**:1293–1303.
23 Vermorken JB, Mesia R, Rivera F, Remenar E, Kawecki A, Rottey S, *et al.* Platinum-based chemotherapy plus cetuximab in head and neck cancer. *N Engl J Med* 2008; **359**:1116–1127.
24 Bernier J, Domenge C, Ozsahin M, Matuszewska K, Lefèbvre JL, Greiner RH, *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**:1945–1952.
25 Panageas KS, Ben-Porat L, Dickler MN, Chapman PB, Schrag D. When you look matters: the effect of assessment schedule on progression-free survival. *J Natl Cancer Inst*. 2007; **99**:428–432.
26 Dancey JE, Dodd LE, Ford R, Kaplan R, Mooney M, Rubinstein L, *et al.* Recommendations for the assessment of progression in randomised cancer treatment trials. *Eur J Cancer* 2009; **45**:281–289.