Original Study

A Statistical Approach to Determine the Optimal Duration of Post-Treatment Follow-Up: Application to Metastatic Nonseminomatous Germ Cell Tumors

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Abstract

As the number of patients in cancer remission increases every year, an economically attractive option is to reduce duration of follow-up according to prognostic factors. In the present study we propose a statistical method to define an optimal duration of follow-up for patients in remission after treatment for cancer, for detection of recurrences.

Background: The objective of this study was to present a statistical method to define an optimal duration of follow-up for patients in remission after treatment for cancer, for detection of recurrences. **Patients and Methods:** Surveillance duration was estimated using the 2-step approach proposed by Mould et al. Relapse-free interval was modeled using the parametric cure model proposed by Boag. The optimal length of follow-up was then estimated as the minimal elapsed time after which the probability of a patient to relapse and to be cured with success is below a given threshold value. The method is applied to 2 real data sets of patients treated for metastatic non seminomatous germ-cell tumors: T93BP and T93MP. **Results:** For the T93BP, cure rate was estimated at 91.3% and proportions of patients who relapsed after 3 and 5 years were estimated at 0.5% and 0.2%. With a probability of success of salvage treatment equal to 80% and 50%, numbers of delayed cases after 5 years were 2 and 1. For T93MP, the proportion of patients who presented relapse after 5 and 10 years were estimated at 5.2% and 2.6%. Considering a probability of salvage treatment equal to 20%, the number of delayed cases after 5 and 10 years were 10 and 5. **Conclusion:** Using this methodology, duration of post-therapeutic follow-up might be tailored according to an objective criteria: the number of patients who present relapse after the end of follow-up and who could have been treated with success in case of early detection.

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Introduction

Nonseminomatous germ cell tumors (NSGCTs) are among the rare cancer types in which a large majority of patients with metastatic disease can be cured.[1] For patients defined as good prognosis according to International Germ Cell Consensus Classification Group (IGCCCG) criteria, the standard treatment is 3 cycles of bleomycin, etoposide, and cisplatin (BEP). For this subgroup of patients, high cure rates are expected,[2] and only 5% to 10% of patients relapse during follow-up. On the contrary, patients categorized as poor prognosis have been associated with a 2-year progression-free survival rate of 41%.[3] Until recently, the standard treatment for poor prognosis patients was 4 cycles of BEP.[4]

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Recently, a trial that compared personalized treatment with chemotherapy intensification to 4 cycles of BEP showed an improvement in progression-free survival and overall survival.[5]

No specific study has addressed the question of optimal follow-up procedures in advanced/metastatic NSGCT. However, several standard follow-up procedures have been proposed in the literature.[6-8] Because most relapses occur during the first 2 years,[2] an intensive schedule is proposed during this period. Different retrospective studies underline a low risk of recurrence after 5 years.[9,10] For this reason, a late follow-up is advocated because late relapses can occur after 5 years for low-risk patients. The South East England Testicular Cancer Supra-regional Network proposed to follow-up patients annually between 5 and 10 years and every 2 years subsequently.[8] The recommended follow-up by the European Association of Urology for metastatic NSGCT is summarized in Table 1.[6] All of these guidelines present the schedule of surveillance for the first 5 years after treatment. Small indication is provided for late surveillance, between year 5 and year 10. Moreover, no advice is given on how long the surveillance should be held.

Ideally, the duration of post-therapeutic surveillance should be individualized. In fact, some patients will never experience relapse but will nevertheless be followed during a long period of time. The pattern of relapse might be different according to prognostic factors: some patients might present relapse earlier after the end of treatment than others. Because the number of patients in cancer remission increases every year, an economically attractive option is to reduce duration of follow-up according to prognostic factors. Ten years ago, Mould et al proposed a statistical approach on the basis of a parametric mixture cure model to reduce duration of follow-up after treatment for early breast cancer.[11] With the objective of a rationalized duration of follow-up, we present the methodology developed by Mould et al and an extension, which permits personalization of the duration of post-therapeutic follow-up. This approach is illustrated on data from 2 clinical trials on metastatic disease for NSGCT.

Patients and Methods

Patient Population

Patient data were obtained from the Genito-Urinary Group of the French Federation of Cancer Centers trials for good prognosis patients (T93BP)[12] and for intermediate- to poor-risk patients (T93MP).[13] Patients had a histologically confirmed nonseminomatous germ-cell tumor with the following features: testicular or retroperitoneal primary, no previous chemotherapy, metastatic disease evidenced by radiographic assessment, or elevated serum tumor marker levels. The 2 groups of patients were then considered as either good or poor risk according to the Institut Gustave Roussy (IGR) prognostic model on the basis of serum α-fetoprotein and human chorionic gonadotropin levels.[14] The trial's inclusion criteria, treatment arms, and results have been extensively described in detail elsewhere.[12,13] At the end of chemotherapy, the surgical resection of all residual masses was performed. Patients were retrospectively assigned into the International Germ Cell Consensus Classification.[15]

Favorable responses were defined by clinical complete response (normal levels of serum tumor markers, no clinical or radiologic evidence of residual disease), surgical complete response (normal levels of serum tumor markers and complete resection of residual masses with persistent viable cancer cells), pathological complete response (normal levels of serum tumor markers and complete resection of residual masses with pathologic analysis revealing necrotic debris, fibrosis, or teratoma), or partial response (inoperable residual mass) with normal levels of serum tumor markers. Any other situation was judged as an incomplete response and patients were excluded from the current study: 24 from T93BP and 84 from T93MP. The study population thus consisted only of patients who presented favorable response: 246 and 106 patients from the T93BP and T93MP trials, respectively. Relapse-free interval was defined as the time interval between end of treatment and relapse. Patients alive at last follow-up or who died before relapse were censored at last follow-up.

Table 1 Recommended Minimum Follow-Up Schedule in Advanced NSGCT

Follow-Up	Year			
	1	2	3 to 5	Thereafter
Clinical Marker Chest X-Ray	4 Times	4 Times	Twice per year	Twice per year
Abdominal Scan	Twice	Twice	As indicated	As indicated
Chest CT Scan	As indicated	As indicated	As indicated	As indicated

Parametric Mixture Cure Models: The Boag Model

After treatment for metastatic NSGCT, patients who presented a favorable response were considered in a remission phase. Many of them did not relapse during follow-up. The other patients presented recurrences a few months or several years after treatment.

In classical survival analysis, it is assumed that all patients present the event of interest if they are followed indefinitely. To relax this assumption, Boag proposed a parametric mixture cure model in which he assumed that a fraction of patients (π) with $0 \leq \pi \leq 1$ were cured of the disease, and the remaining patients recurred.[16] He performed the hypothesis that time before recurrence in the second fraction of patients $(1 - \pi)$ follows a log-normal distribution. The mathematical expression of the survival function at time t [S(t)] in the Boag model was:

$$S(t) = \pi + (1 - \pi)(1 - F_R(t))$$

where F_R is the cumulative distribution function of a log-normal distribution with mean μ and standard deviation σ. The 3 parameters were directly estimated using maximum likelihood.[17]

An extension of this methodology allows the inclusion of covariates in the model to identify prognostic factors associated with failure time and cure rate.[18] The covariates associated with failure time and cure can be distinct. The mean of the log-survival time was defined by $\mu = \alpha_T + \beta'_T X_T$ with X_T the vector of covariates, α_T the intercept, and β'_T the vector of regression coefficients. The cure fraction was modeled using logistic link regression:

$$\pi = 1/\left[1 + \exp\left(-\alpha_c - \beta'_c X_c\right)\right]$$

with X_c the vector of covariates, α_c the intercept, and β'_c the vector of regression coefficients. Covariate effects associated with cure rate were interpreted in a similar way as in logistic regression.