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THÈSE

En vue de l'obtention du

DOCTORAT DE L'UNIVERSITÉ DE TOULOUSE

Délivré par : *l'Université Toulouse 1 Capitole (UT1 Capitole)*

Présentée et soutenue le *15 septembre 2015* **par :**

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Individualisation du suivi post-thérapeutique des patients traités du cancer en fonction des facteurs pronostiques et du type de rechute.

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À Johann
Joëlle

Malgré les premiers jours à l'école manqués,
Malgré les anniversaires manqués,
Malgré les grandes joies, ...
les grandes frayeurs ...
vécues seuls, et moi toujours loin,
Vous faites toujours montre de soutien et de solidarité...
Papa rentre à la maison.

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Introduction

I Le cancer dans le monde

Le cancer est un terme générique employé pour caractériser un large groupe de maladies pouvant affecter n'importe quelle partie de l'organisme. Les termes de tumeurs malignes ou de néoplasmes sont aussi employés [1]. Une caractéristique du cancer est la création rapide de cellules anormales qui croissent au-delà de leur taille usuelle et qui peuvent ensuite envahir des parties proches du corps et se répandre dans d'autres organes. Ce sont les métastases. Les métastases sont les principales causes de décès du cancer.

Le cancer est, d'après l'Organisation Mondiale de la Santé [1], la première cause de décès dans le monde. En effet, 8,8 millions de décès dus au cancer ont été enregistrés en 2012 [2] dont les principales localisations étaient :

- *le cancer du poumon* : 1,59 millions de décès,
- *le cancer du foie* : 745 000 décès,
- *le cancer de l'estomac* : 723 000 décès,

– *le cancer colorectal* : 694 000 décès,
– *le cancer du sein* : 521 000 décès,
– *le cancer de l'œsophage* : 400 000 décès.

Dans leur revue, Siegel *et al.* [3] ont fait un point sur l'importance du cancer aux États-Unis où une femme sur trois et un homme sur deux auront un cancer au long de leur vie. La figure I.1 représente l'estimation du nombre de personnes vivant avec la maladie selon la localisation de leur cancer en 2012 et une projection en 2022.

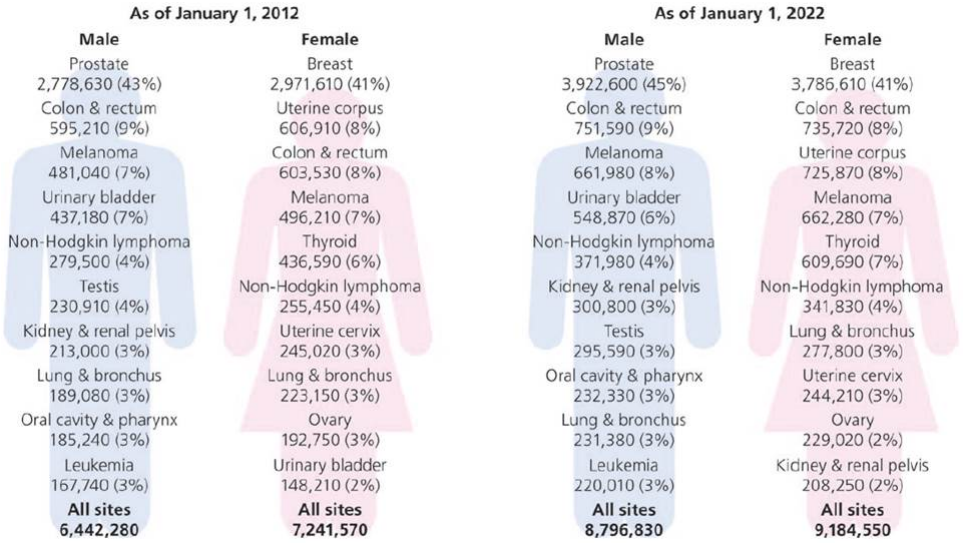

FIGURE I.1 – Estimation du nombre de personnes vivant avec un cancer aux États-Unis par localisation en 2012 et projection en 2022 [3]

La lutte contre le cancer dans le monde prend plusieurs formes, à plusieurs étapes de la maladie. Cette lutte se mène à travers la mise en œuvre de stratégies probantes, définies par l'Organisation Mondiale de la Santé, pour la prévention, la détection précoce et la prise en charge des patients [1] :

Modifier et éviter les facteurs de risque : plus de 30% des décès liés au cancer pourraient être évités en évitant ou en modifiant les facteurs de risque suivants :
– l'usage du tabac ;
– le sur-poids ou l'obésité ;
– l'alimentation déséquilibrée avec de faibles prises de fruits et légumes ;
– la sédentarité ;

- l'usage de l'alcool ;
- l'infection par virus de l'hépatite B ;
- les radiations ionisantes et non ionisantes ;
- les fumées à l'intérieur des habitations dues à l'utilisation de combustibles solides par les ménages.

Stratégies de prévention : les actions suivantes sont entreprises :

- accroître la lutte contre les facteurs de risque cités ci-dessus ;
- vacciner contre le virus du papillome humain et le virus de l'hépatite B ;
- contrôler les risques professionnels ;
- réduire l'exposition aux radiations non ionisantes par le soleil (UV) ;
- réduire l'exposition aux radiations ionisantes (professionnelle ou diagnostic par imagerie médicale).

Détection précoce : la mortalité due au cancer peut être réduite si les cas sont détectés et traités assez tôt. La détection précoce s'organise à travers le diagnostic précoce et le dépistage.

Le diagnostic précoce consiste en la recherche de signes ou de symptômes précoces (pour les sites tels que la peau, le col de l'utérus, le sein, le colon, la tête ou le cou) afin de permettre un diagnostic et un traitement en phase précoce. Le dépistage vise à identifier les individus présentant des caractéristiques suggérant un cancer ou un pré-cancer spécifique et de les référer rapidement pour un traitement. En absence de détection ou de diagnostic précoce avec une intervention thérapeutique, les patients sont diagnostiqués à des stages très tardifs quand les traitements curatifs ne sont plus possibles.

Traitement curatif : l'objectif primaire des traitements est de guérir le cancer ou de prolonger de façon considérable la durée de vie. Ces traitements sont composés de une ou de plusieurs séquences de chirurgie, de radiothérapie et/ou de chimiothérapie. Améliorer la qualité de vie est aussi un but important. Ceci peut être atteint par un accompagnement de soutien ou palliatif ainsi qu'une prise en charge psychologique.

Prise en charge palliative : les traitements palliatifs ont pour but de soulager, à défaut de guérir les symptômes causés par le cancer. Ceux-ci permettent aux patients de vivre plus confortablement. Ils sont le plus souvent utilisés lorsque les patients atteignent un stade avancé où ils ont de faibles chances d'être guéris.

II Problématique

Les patients en rémission à la suite d'un traitement curatif du cancer entrent dans une phase dite de surveillance post-thérapeutique. Cette phase vise à déceler les rechutes à un stade précoce, afin de proposer des traitements, curatifs ou palliatifs. Elle repose notamment sur des examens cliniques, de l'imagerie, éventuellement des endoscopies et des études de marqueurs biologiques. Le suivi permet également de mesurer les conséquences du traitement, à plus ou moins long terme, tant sur le plan de l'efficacité que de la tolérance.

La surveillance post-thérapeutique vise plusieurs autres objectifs aussi importants que la détection des récidives : (i) la réinsertion sociale et la réhabilitation du patient [4] ; (ii) l'évaluation économique de l'utilisation optimale des ressources [5] ; (iii) l'amélioration des connaissances sur le diagnostic et le traitement [6].

Afin de maximiser l'efficacité du suivi des patients, les visites devraient être les plus nombreuses possibles. Ceci n'est cependant pas possible pour des raisons pratiques et de coût. Il est alors nécessaire de déterminer un calendrier de surveillance. Ce calendrier devra proposer des visites suffisamment fréquentes mais aussi en nombre suffisamment réduit afin de limiter la charge aussi bien pour le patient, le praticien que l'établissement de soins. Différentes sociétés spécialisées ont proposé des calendriers de surveillance pour les différentes pathologies, visant à allier efficacité diagnostique, coût du traitement, qualité de vie et coût global. Des recommandations sont émises pour des localisations telles que le sein [7–9], le poumon [10], les sarcomes [11], le cancer colorectal [12, 13], etc. Ces différentes planifications sont cependant généralement définies sur la base d'avis d'experts, sans évaluation reposant sur un essai clinique randomisé.

La définition d'un protocole de surveillance thérapeutique qui réponde à tous les besoins contemporains en termes de qualité et d'efficacité de soins devrait passer par la

réponse aux deux questions capitales suivantes :

1. *Pendant combien de temps surveiller un patient ?*
2. *Quand programmer les visites de surveillance ?*

Les réponses à ces questions sont d'autant plus complexes que celles-ci dépendraient du type de cancer et de sa gravité, ainsi que des caractéristiques individuelles des patients. Plusieurs praticiens adaptent d'ailleurs les rythmes de surveillance selon leur expérience propre, s'éloignant parfois des recommandations qu'ils trouvent trop peu adaptées [14]. Plusieurs méthodes pour l'organisation des calendriers de surveillance post-thérapeutique sont inspirées de travaux effectués dans le cadre de la planification du dépistage. Les avancées dans ce domaine sont en effet plus précoces et plus significatives.

II.1 La problématique du dépistage du cancer

Histoire naturelle de la maladie

La modélisation de l'histoire naturelle du cancer dans le cadre du dépistage de la maladie a été largement étudiée dans la littérature. Les approches simplifiées de l'histoire naturelle de la maladie sont généralement représentées en quatre états. Le premier état représente le statut sain où le sujet n'a aucune tumeur. Cet état peut aussi correspondre à une tumeur naissante toujours à un stage non détectable par les techniques de dépistage ou de diagnostic. L'état suivant est celui du passage en phase pré-clinique. A ce moment, la tumeur a atteint une taille telle qu'elle peut être détectée par les technologies existantes, ou les marqueurs biologiques ont atteint un niveau de sorte à permettre la détection d'un cancer. Le patient ne présente à ce moment aucun symptôme de sa maladie et celle-ci ne peut être détectée. La phase suivante de l'histoire de la maladie est sa phase clinique. Il s'agit de la phase d'apparition des symptômes. Le patient ayant atteint cette phase est généralement diagnostiqué après une visite médicale. Enfin, le dernier état est le décès qui est un état absorbant.

Une des nombreuses illustrations de l'histoire naturelle dans le cas du dépistage est proposée par Van Oormarssen *et al.* [15] dans la figure I.2. La plus grande majorité des personnes n'auront jamais d'épisode cancéreux et connaîtrons seulement deux états,

l'état SAIN et l'état DÉCÈS D'AUTRE CAUSE. Les personnes qui auront une tumeur cancéreuse passeront par CANCER NON DÉTECTABLE à CANCER DÉTECTABLE en phase pré-clinique qui sera toujours indétectable en absence de dépistage (asymptomatique). Le cancer ne pourra être diagnostiqué que lorsqu'il commencera à présenter des symptômes (STADE CLINIQUE INVASIF), et des traitements appliqués à ce moment pourront conduire à la guérison du patient ou pourront être sans succès et la personne mourra de cancer (DÉCÈS DÛ AU CANCER). Le dépistage devrait permettre de détecter des cas dans la phase CANCER DÉTECTABLE NON INVASIF et CANCER DÉTECTABLE INVASIF. L'efficacité du dépistage se retrouve dans l'amélioration des pronostics de guérison et de la survie entre des cancers dépistés et des cancers diagnostiqués en phase cliniquement.

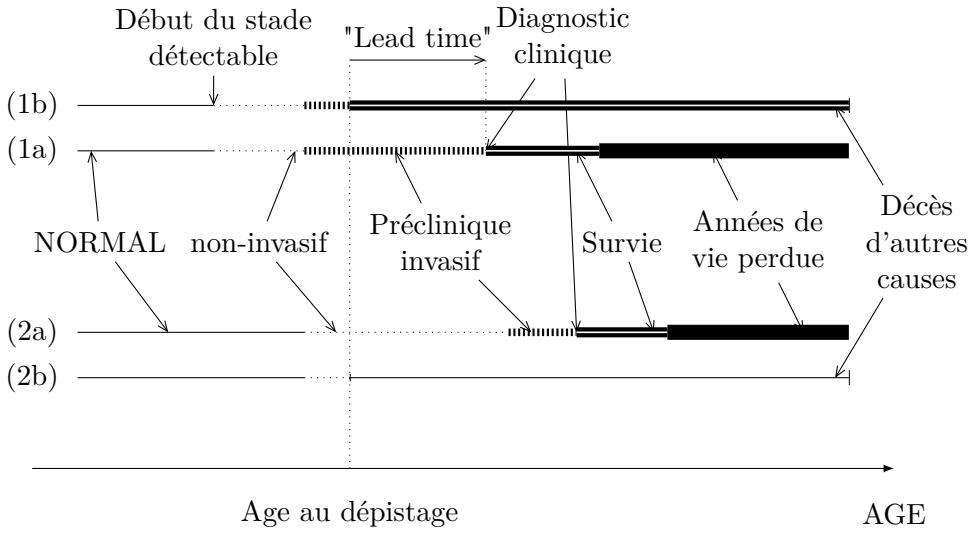

FIGURE I.2 – Exemple de deux histoires naturelles de base pour le dépistage du cancer : (1) et (2), et les effets de la détection par dépistage. (1a), (2a) : pas de dépistage, la personne meurt du cancer ; (1b) : cancer dépisté à un stade invasif, la personne survit jusqu'au décès d'autre cause ; (2b) : cancer dépisté à un stade pré-clinique, guérison [15].

Zelen et Feinleib [16] ont très tôt défini une approche théorique pour modéliser l'histoire naturelle des cancers. Leur modèle inclut la date de détection précoce, le délai avant le dépistage et permet d'évaluer le bénéfice du dépistage. Ils spécifiaient par ailleurs [17] les embûches éventuelles en reproduisant cet exercice. Plusieurs modèles ont ensuite permis d'estimer le temps de séjour dans les différents états, notamment le temps moyen

de séjour en phase pré-clinique, en prédisant la mortalité, l'incidence et la réduction de mortalité due au dépistage [18, 19], en utilisant des processus Markoviens [20] ou des distributions non-homogènes [21]. Cette approche de modélisation a été largement utilisée, notamment par Shen et Zelen [22]. C'est par ailleurs l'approche clinique utilisée pour décrire le processus du cancer.

Eddy [23] a discuté de l'utilisation des modèles mathématiques pour mieux comprendre les phénomènes biologiques complexes. Il a aussi fait ressortir la principale difficulté dans ces cas qui est de confirmer les modèles sur la base des résultats. En faisant cet exercice, il a validé les résultats d'un modèle mathématique sur des données empiriques.

Stratégies de dépistage

Alors que Kirch et Klein [24, 25] ont discuté de l'organisation des calendriers de surveillance à partir des modèles mathématiques, Zelen [26] propose une approche stochastique pour déterminer un calendrier optimal pour le dépistage du cancer du sein. Il définit une fonction d'utilité dépendant de n dates de visites réparties dans la période de surveillance. Le calendrier de surveillance optimal est celui composé des n dates maximisant cette fonction. Une adaptation, moins efficace en termes d'utilités mais plus pratique pour la programmation, est proposée avec des visites à intervalles réguliers. D'autres propositions sont disponibles dans la littérature pour la programmation du dépistage. Celle basée sur la valeur seuil [27, 28] consiste à modéliser la probabilité de développer un cancer en phase pré-clinique depuis la dernière visite et de programmer une autre visite dès que cette probabilité atteint un certain seuil. Les approches mathématiques pour une stratégie optimale de dépistage sont ensuite largement développées [29–32]. Elles sont de plus étendues à l'estimation des temps d'examens dans d'autres maladies [33].

Finalement la recherche pour améliorer les stratégies de dépistage du cancer a pris l'option de considérer la dynamique de ces examens [34], avec notamment les modèles joints de croissance tumorale [35].

II.2 La problématique du suivi post-thérapeutique

Histoire naturelle de la maladie

La modélisation de la surveillance post-thérapeutique des patients traités du cancer connaît moins d'engouement que celle du dépistage, même si celle-ci n'est pas négligeable. Un certain nombre de différences existent pour la modélisation.

Dans le cadre du dépistage du cancer, la date de début n'est pas fixe. Certains auteurs considèrent la date de naissance pour la modélisation [18]. La variable temps correspond par suite à l'âge du patient (figure I.2). Il arrive parfois d'utiliser une autre date telle que l'atteinte d'un âge donné ou la date d'exposition à un facteur de risque donné. Dans le cas de l'histoire naturelle de la surveillance, celle-ci commencera à la date de fin du traitement.

La deuxième différence fondamentale entre le dépistage et la surveillance est que dans le cas du dépistage, un événement unique est observé qui est l'apparition du cancer. Pour ce qui concerne la surveillance, plusieurs types d'événements peuvent être considérés. En effet, alors que l'on pourrait chercher à détecter une récidive locale de façon précoce [36], il serait encore plus intéressant de prendre en compte différents type de rechute possibles [37]. En effet, un patient en phase de rémission est à risque de récidive de type locale ou ganglionnaire, d'apparition d'un second cancer ou de métastase à distance pour ce qui concerne le cas général. Les distributions des risques d'apparition de ces différents types de récidive sont généralement différentes. Ces événements peuvent être considérés comme concurrents si seulement le premier type de récidive est considéré. Par contre, en considérant l'histoire naturelle dans son ensemble, jusqu'au décès, l'on se retrouve dans un système multi-états. Le schéma de la figure I.3 proposé par Ritoe *et al.* [38] présente l'histoire naturelle de la maladie après un traitement d'un carcinome épidermoïde localement avancé de la tête et du cou. Il présente trois types de récidives, à savoir la récidive loco-régionale, la métastase et le second cancer ORL. Les stades asymptomatiques (pré-cliniques) et symptomatiques (cliniques) sont aussi distingués.

Dans le cas où plusieurs types de récidives sont considérés, la surveillance devrait de plus être adaptée à chaque type de récidive d'autant plus que le clinicien n'a pas le même intérêt pour un dépistage précoce d'une récidive locale qui pourrait être bien soignée que pour celui d'une métastase incurable [40].

Il faut noter qu'une modélisation de l'histoire de la maladie dans le cadre de la surveillance post-thérapeutique s'avère souvent bien plus complexe en prenant en compte

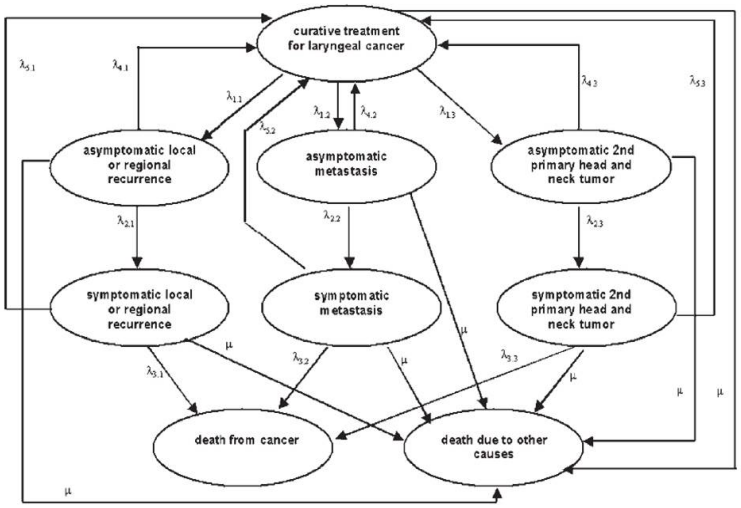

FIGURE I.3 – Modèle de Markov représentant l'histoire de patients traités d'un cancer laryngé. La lettre λ indique le risque de progression de la maladie, les i dans λ_{ij} se réfère à la progression d'un état à un autre tandis que j indique le type de récidive (loco-régionale, métastatique ou second cancer primaire de la tête ou du cou) [39].

les co-morbidités. Dans ce cas, les états spécifiés ne sont plus disjoints mais présentent des interactions.

Stratégies de suivi

Les calendriers utilisés pour le suivi post-thérapeutique des patients traités du cancer doivent être optimisés. Francken *et al.* [41, 42] ont montré que dans le cadre des mélanomes, trois quart des récidives sont encore détectées par les patients ou leur entourage, pour beaucoup, après l'apparition des symptômes. Plusieurs auteurs ont pu observer que le pronostic de survie était meilleur quand le diagnostic était réalisé à un stade asymptomatique [43, 44]. Ces récidives sont diagnostiquées à des stades avancés, ce qui réduit considérablement le pronostic de guérison.

D'autre part, étant donné le nombre croissant de patients en phase de suivi, les coûts liés à celle-ci sont importants. Hofmann *et al.* [45], après avoir analysé les données de 661 patients traités pour un mélanome en Allemagne entre 1983 et 1999, ont estimé que le coût moyen de la surveillance pour détecter une récidive avait varié de 5 806€ (écart type 1 289€) entre 1983 et 1987 et de 18 558€ (écart-type 6 706) entre 1987 et 1990, les

surveillances les plus coûteuses étant celles pour lesquelles les risques de rechutes sont les moins élevés. Il est alors évident que l'adaptation du suivi aux risques de rechute permet un contrôle plus important de ces coûts.

En se basant sur ce principe, Wheeler *et al.* [46] ont proposé une méthode en deux étapes de planification des visites. Ils estiment dans un premier temps les risques de récidive. Ils définissent ensuite un calendrier s'adaptant à ces estimations. Tsodikov *et al.* [47] ont estimé les délais avant récidive et les probabilités de diagnostics faux positifs par modélisation stochastique. Des méthodes bayésiennes ont aussi été proposées, notamment par Inoue et Parmigiani [48], mais celles-ci sont difficiles à mettre en œuvre. Mould *et al.* [36] proposent, quant à eux, de réduire la durée totale de la surveillance sans augmenter de façon significative la probabilité que des patients suivis rechutent après la fin de celle-ci alors qu'ils auraient pu être pris en charge avec succès. Enfin, Filleron *et al.* [37] ont proposé un algorithme en deux étapes pour définir un rythme pour la programmation des visites, en se basant sur les caractéristiques individuelles. Dans la première étape, ils identifient les facteurs pronostiques du délai avant la récidive. Ensuite, ils modélisent l'incidence cumulée en fonction de ces facteurs de risque. Les dates des visites sont alors déterminées en fonction des quantiles de cette fonction d'incidence cumulée.

Les méthodes proposées ne prennent cependant pas en compte les différentes étapes de l'histoire naturelle de la récidive, en distinguant les stades pré-cliniques des stades cliniques de la maladie. Des hypothèses de simplification pourraient être faites pour incorporer cette histoire naturelle dans la modélisation, au même titre que dans le cas du dépistage, afin de permettre la définition d'outils d'aide à la décision qui puissent être implémentés dans les systèmes de santé.

III Objectifs et plan

La présente thèse a pour objectif de proposer des outils d'aide à la décision pour la détermination de stratégies individualisées de suivi de patients en phase de rémission après un traitement curatif de cancer primaire. Ce suivi devrait prendre en compte les types d'événements auxquels le patient serait toujours à risque ainsi que les caractéristiques

individuelles (facteurs pronostiques) de celui-ci. En ce sens, trois objectifs spécifiques se dégagent. Il s'agit de proposer des outils pouvant permettre de répondre aux trois questions clés, à savoir :

1. Pendant combien de temps surveiller un patient en phase de rémission en considérant :
   - le type et la gravité de son cancer ;
   - ses caractéristiques individuelles ;
   - les différents types de rechute auxquels il est à risque ;
   - les probabilités de guérison en cas de détection précoce et de traitement de ces différentes récidives.

2. Quelle est la programmation optimale des visites de suivi pour un patient en phase de surveillance en considérant :
   - la durée maximale de suivi ;
   - le nombre de visites programmées ;
   - le risque d'apparition d'une récidive d'un type donné ;
   - les probabilités de guérison en cas de détection précoce et de traitement de ces différentes récidives ;
   - le risque de passage à une phase clinique d'une récidive d'un type donné non détectée en phase précoce ;
   - les probabilités de guérison en cas de traitement de ces différentes récidives, en phase précoce.

3. Comment comparer l'effet sur la survie des patients de deux stratégies de surveillance post-thérapeutique par simulation numérique en considérant :
   - la sensibilité des examens de suivi ;
   - l'observance des stratégies de surveillance ;
   - le risque d'apparition d'une récidive d'un type donné ;
   - le risque de passage à une phase clinique d'une récidive d'un type donné non détectée en phase précoce.

Le présent document rassemble les résumés de travaux publiés ou soumis à publication dans des revues internationales à comité de lecture spécialisées en aide à la décision

en médecine, en méthodologie biostatistique ou en clinique. Le chapitre II présente une application de l'approche de Mould *et al.* [36] pour déterminer la durée de suivi optimale de patients traités d'une tumeur germinale du testicule. Des règles de décision sont proposées pour les patients en fonction de leur pronostic et de leur réponse au traitement. L'approche de Mould *et al.* [36] a ensuite été généralisée pour prendre en compte plusieurs événements à risque. Pour un patient donné, lorsque la durée de suivi ainsi que le nombre de visites ont été arrêtés par le médecin, l'approche décrite dans le chapitre III permet de déterminer les dates optimales auxquelles les visites devraient être programmées pour une utilité maximale de la stratégie de surveillance.

Plusieurs stratégies peuvent être proposées pour la surveillance d'un cancer donné. L'évaluation de celles-ci par un essai clinique, afin de déterminer la plus efficace, poserait cependant plusieurs difficultés tant éthiques que logistiques. Dans le chapitre IV est proposé un algorithme permettant d'effectuer cette évaluation au moyen des outils de simulation numérique. Enfin, le dernier chapitre discutera de l'ensemble des méthodes et permettra de tirer les conclusions du travail.

Chapitre II

Détermination de la durée de surveillance post-thérapeutique optimale

I Problématique

Les différentes recommandations sur le suivi des patients atteints du cancer [9, 13, 49] proposent généralement des calendriers de visites spécifiques pour les cinq premières années après le traitement. Au-delà de cinq ans, les calendriers proposent le plus souvent d'organiser une visite chaque année. Ces recommandations ne précisent cependant pas pendant combien de temps le patient devra être suivi [50]. Les stratégies de surveillance post-thérapeutique sont généralement fondées sur les connaissances de l'histoire naturelle de la maladie. les patients sont habituellement suivis selon un rythme rapproché dans les premières années en raison de pics de récidive souvent observées. Le suivi est par la suite de moins en moins intensif étant donnée la baisse de la fréquence des récidives. Finalement, après un certain temps, le nombre de patients toujours à risque de récidive sera suffisamment faible pour que la surveillance ne soit plus requise. Il est donc

important de déterminer la durée optimale du suivi.

Un tel exercice passerait par la modélisation de la date d'apparition de la récidive. Cependant, les modèles classiques de survie sont difficilement applicables à la surveillance post-thérapeutique. En effet, ces modèles considèrent que si tous les patients sont suivis jusqu'à l'infini, 100% d'entre eux réaliseront l'événement. Dans le cas de la surveillance cependant, une fraction de la population, après le traitement, n'observera jamais de rechute, quelle que soit la durée de suivi. Cette fraction de la population est considérée comme *guérie*.

Plusieurs approches proposent une évaluation en deux étapes pour modéliser la durée avant une rechute en présence de guérison. Une première étape sera la détermination du taux de guérison. Celui-ci peut être estimé par la méthode de Kaplan-Meier [51]. En prenant en compte la survie relative [52], il est égal au rapport entre la survie observée chez les patients après la période d'observation (généralement cinq années) et celle observée dans un groupe comparable de la population générale [53]. Cependant « *définir la guérison comme le fait de ne pas mourir d'un cancer dans les cinq années suivant le traitement est optimiste, la mortalité par cancer entre 5 et 10 ans après le traitement n'est en effet pas complètement négligeable.* » [54]. Récemment, Ambrogi *et al.* [55] ont utilisé une approche par les risques compétitifs pour l'estimation de ce taux de guérison en comparant les mortalités spécifiques.

Boag [56] a proposé dès 1949 un modèle de survie intégrant directement la guérison. Il s'agit d'un modèle de mélange qui permet l'estimation à la fois de la distribution de la récidive et du taux de guérison. Mould *et al.* [36] se sont ensuite inspirés de ce modèle pour proposer une stratégie de détermination de la durée de suivi de patientes traitées pour cancer du sein en stade précoce.

II Approche de Mould

II.1 Objectifs

L'approche décrite par Mould *et al.* [36] est présentée dans cette section. Celle-ci définit une règle de décision permettant de déterminer la durée de surveillance post-thérapeutique. L'objectif de la surveillance dans le cadre du cancer du sein est la détection

précoce d'une récidive locale afin de proposer un traitement curatif. L'approche proposée est en deux étapes : (1) modéliser le délai avant l'apparition de la récidive locale, (2) définir la durée de surveillance en fonction de la distribution de ce délai. La méthode décrite par Mould *et al.* [36] va être présentée puis appliquée à un exemple sur le cancer du testicule en stade avancé.

II.2 Le modèle de Boag

Le modèle de Boag [56] suppose qu'une proportion $\pi \quad (0 \leq \pi \leq 1)$ de patients est guérie et qu'une proportion $(1 - \pi)$ récidivera. Pour ce second groupe, la fonction de répartition associée à l'apparition d'une récidive est modélisée par une loi log-normale et sera notée F_R. La fonction de survie sans récidive s'exprime alors comme un modèle de mélange :

$$S(t) = \pi + (1 - \pi)S_R(t) \tag{II.1}$$

où $S_R(t) = 1 - F_R(t)$ est la fonction de survie sans récidive dans la sous-population des individus qui ne sont pas guéris.

La fonction F_R étant une fonction de répartition, il s'en suit que :

$$\lim_{t \to +\infty} F_R(t) = 1$$

et par conséquent $\lim_{t \to +\infty} S(t) = \pi$.

La droite horizontale d'équation $y = \pi$ est donc une asymptote horizontale à la courbe de la fonction de survie. Cette quantité représente le taux de guérison après le traitement. Pour un taux de guérison nul, c'est-à-dire $\pi = 0$, tous les patients finiront par observer une récidive. Par contre, si le taux de guérison est de 100%, c'est-à-dire $\pi = 1$, tous les patients sont guéris de leur cancer après traitement et aucun événement ne sera observé. Le risque de rechute est donc égal à zéro.

La figure II.1 représente la fonction de survie dans le cas d'un modèle de Boag de paramètres $\mu = 3$, $\sigma = 0,5$, où μ et σ sont respectivement l'espérance mathématique et la variance du logarithme de la durée de suivi, en considérant une probabilité de guérison à la suite du traitement de $\pi = 0,25$.

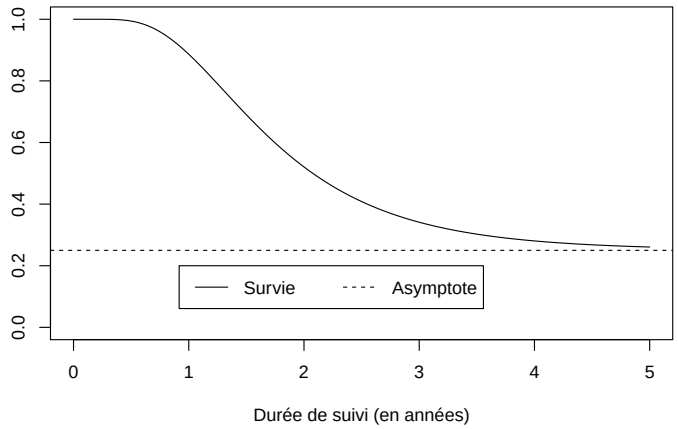

FIGURE II.1 – Exemple de fonction de survie du modèle de Boag

Dans le cas où la distribution log-normale n'ajuste pas correctement les données, des variantes du modèle de Boag ont été proposées dans la littérature. A la place de la distribution log-normale, Sposto [57] propose d'utiliser une distribution de Weibull. Gamel et Vogel [58] reprennent le modèle de mélange en incorporant une distribution log-logistique ou une distribution de Weibull. Peng *et al.* [59] proposent une famille généralisée de modèles à laquelle on peut associer des effets aléatoires [60, 61]. La distribution des événements peut dépendre de facteurs pronostiques qui pourront être pris en compte dans le modèle [57, 60, 61].

Le taux de guérison peut aussi être différent selon les populations de patients. Il est donc possible de l'estimer en fonction des facteurs pronostiques. Il s'exprime alors comme une fonction des covariables et des paramètres de régression associés. Les fonctions envisageables sont les fonctions linéaire, log-log et logistique [59–62].

$$\pi(Z_\pi, \beta_\pi) = \begin{cases} \beta'_\pi Z_\pi & linéaire \\ \frac{exp(\beta'_\pi Z_\pi)}{1-exp(\beta'_\pi Z_\pi)} & logistique \\ exp(-exp(\beta'_\pi Z_\pi)) & log-log \end{cases} \tag{II.2}$$

Plusieurs procédures de type EM (Expectation-Maximization) ont été développées pour l'estimation des paramètres de ces modèles [60, 61, 63, 64]. Celles-ci sont implé-

mentées dans les logiciels statistiques les plus courants [65–67].

II.3 Détermination de la durée de suivi

La fonction de survie sans récidive étant décroissante au cours du temps, il est alors logique de chercher à déterminer un temps à partir duquel le nombre probable de récidives peut être considéré comme négligeable. Si π est la fraction de patients qui ne récidiveront jamais et $S(t)$ la fraction de patients qui n'ont pas récidivé à la date t, alors la proportion de patients qui récidiveront après un temps supérieur à t est $S(t) - \pi$. L'objectif est donc de déterminer un temps de suivi minimal t_{min} tel que $S(t_{min}) - \pi$ soit en-dessous d'un taux de récidives ε acceptable. Cela permettra de proposer une durée de suivi réduite permettant de détecter l'essentiel des événements.

Toutes les récidives ne sont pas traitées avec succès lorsqu'elles sont détectées. Soit ν, $0 \leq \nu \leq 1$, le paramètre défini comme la probabilité d'être traité avec succès en cas de récidive. La probabilité d'avoir un événement et d'être traité avec succès devient $\nu(1-\pi)$ où π est la probabilité de ne jamais récidiver. Le diagramme II.2 permet de définir les différentes catégories et leur probabilité.

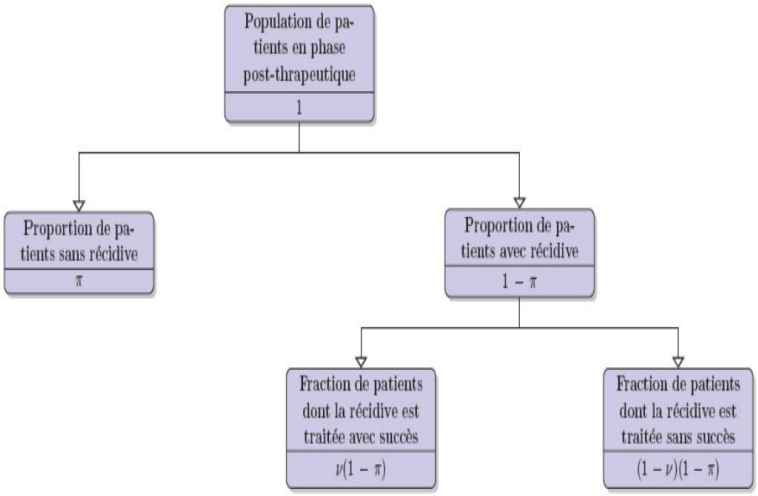

FIGURE II.2 – Diagramme des différentes issues du traitement [36]

En utilisant le modèle de mélange pour estimer $S(t)$, on peut avoir une estimation, pour une durée de surveillance donnée, de la fraction des patients traités avec succès en cas de récidive. On estime alors la fraction de patients qui récidiveront après la fin du

suivi et qui auraient pu être traités si le suivi ne s'arrêtait pas à t :

$$\varepsilon(t) = \nu \times [S(t) - \pi] \tag{II.3}$$

Mould *et al.* [36] ont appliqué leur méthode à une population de femmes traitées pour un cancer du sein. La durée maximale d'observation classiquement appliquée pour détecter les récidives locales était de 10 ans. La fonction de survie sans rechute dans la population susceptible de rechuter valait 10% à 4 ans, c'est-à-dire $S_R(4) = 0,10$. En posant $\pi = 0,85$ et $\nu = 0,80$, pour une durée de suivi de 4 ans, la fraction de patients qui auront une récidive après la fin du suivi et qui auraient pu être traités vaut :

$$\begin{aligned}
\varepsilon(4) &= \nu \times [S(4) - \pi] \\
&= \nu \times [(\pi + (1 - \pi) \times S_R(4)) - \pi] \\
&= 0,80 \times [(0,85 + (1 - 0,85) \times 0,10) - 0,85] \\
&= 0,012
\end{aligned}$$

Cela signifie qu'en suivant les patientes traitées du cancer du sein pendant 4 ans au maximum, sur 1000 patients, 12 patientes auront des récidives locales après la fin du suivi alors qu'elles auraient pu être traités avec succès si cette récidive avait été dépistée.

II.4 Article : application aux tumeurs germinales

Les tumeurs germinales du testicule représentent à peu près 1% de tous les cancers nouvellement diagnostiqués chez l'homme et étaient la cause de 10 000 décès en 2012 [68]. Le cancer du testicule est un cancer de bon pronostic, y compris en situation métastatique. La survie relative à 5 ans est de 98-99% pour les formes localisées et supérieur à 70% pour les formes métastatiques. Les tumeurs germinales non séminomateuses (TGNS) correspondent à 40% des tumeurs germinales [69].

L'article présenté donne des indications sur l'individualisation de la durée de suivi des patients traités de TGNS en phase métastatique. Les données utilisées sont issues de deux essais cliniques du Groupe Génito-Urinaire de la Fédération Française des Centres

de Lutte Contre le Cancer pour les patients de bon pronostic (Essai GETUG T93BP [70]) et pour les patients de pronostic intermédiaire à mauvais (Essai GETUG T93MP [71]).

A statistical approach for post-therapeutic follow-up schedules: example on metastatic nonseminomatous germ-cell tumors

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Abstract

The objective of this study was to present a statistical method to define an optimal duration of follow-up for patients in remission after a treatment for cancer, for detection of recurrences. The approach described by Mould et al. is presented. This two-step method, first models the long term relapse free survival, using a Boag mixture cure model with a log normal distribution. The length of follow-up is 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 on two real data sets of patients treated for metastatic nonseminomatomous germ-cell tumors. The number of analyzed observations is 246 good prognosis patients and 106 poor prognosis patients according to the Institut Gustave Roussy prognostic system. Finally, the length of follow-up could be tailored according to the type of response to treatment for the good prognosis patients, where patients with a complete response to treatment could have a lighter surveillance program. The schedule applied to poor prognosis patients could also be tailored according to the disease classification.

Keywords: Cancer; follow-up; Cure model; log-normal; testis.

Introduction

Improving survival after cancer treatment is an important issue during the post-therapeutic follow-up phase. In fact, the main objective of post-therapeutic follow-up is to detect recurrence early enough in order to propose salvage treatment with a curative intent. Considering this objective, different societies as the American Society of Clinical Oncology, the European Society of Medical Oncology and others, have proposed surveillance calendars for different cancer sites (1,2). These schedules are planned at regular intervals and include clinical examinations, imagery, and/or biological markers. However, recurrence times do not all occur with the same intensity (3). Certain patients will never experience relapse but will nevertheless be followed during a long period of time. Ideally, the duration of post-therapeutic surveillance should take into account the probability of relapse. As the number of patients in cancer remission increases every year, an economically attractive option is to reduce duration of the follow-up. An important question is “At which year can post-treatment follow-up be stopped?” A statistical approach based on a parametric mixture cure model was proposed to reduce the duration of follow-up after treatment for early breast cancer (4). This approach, determines duration of post-therapeutic follow-up according to the probability of observing the event of interest. This concept, based on a mathematical formula, can be used for other cancer sites (5).

Non Seminomatous Germ Cell Tumors (NSGCT) are among the rare cancer types where a large majority of patients with metastatic disease can be cured (6). For patients defined as good prognosis by International Germ Cell Consensus Classification Group (IGCCG), the standard treatment is 3 cycles of bleomycin, etoposide and cisplatin (BEP). For this subgroup of patients high cure rates are expected (7), 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% (8). Until recently, the standard treatment for poor prognosis patients has been four cycles of BEP (9). Recently, a trial comparing personalized treatment with chemotherapy intensification to four cycles of BEP showed an improvement in progression free survival and overall survival (10). 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 (11,12).

As the majority of relapses occur during the first two years (6), an intensive schedule is proposed during this period. Different retrospective studies underline a low risk of recurrence after five years (13,14). For this reason, a late follow-up is advocated since late relapses can

occur after 5 years for low risk patients. The South East England Testicular Cancer Supra-regional Network proposed to follow patients up annually between 5 and 10 years and every 2 years subsequently (12). Table 1 summarizes the recommended follow-up by the European Association of Urology (EAU) for metastatic Non Seminomatous Germ Cell Tumors (15). All these guidelines present the rhythms of surveillance for the first five years after treatment. Small indication is provided for late surveillance, between year five and year ten. However, no advice is given on how long should the surveillance be held. The main objective of this publication is to present the methodology proposed by Mould (4) to determine duration of post-therapeutic follow-up and to illustrate it on data from two clinical trials on metastatic disease for NSGCT.

Patients and Methods

Patient Population

Patient data was obtained from the Genito-Urinary Group of the French Federation of Cancer Centers Trials for good prognosis patients (GETUG T93BP) (16) and for intermediate to poor risk patients (GETUG T93MP) (17). 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 raised serum tumor markers. The two groups of patients were then considered as either good or poor risk according to the Institut Gustave Roussy prognostic model based on serum AFP and HCG levels (18). In the T93BP trial (16), good risk patients were randomized between three cycles of bleomycin (Sanofi-Aventis, France) (30 IU on days 1,8 and 15), etoposide (Merck, France) (100 mg/m2 on days 1-5) and cisplatin (Merck, France) (20mg/m2 on days 1-5), namely BEP or four cycles of the same regiment without bleomycin. Each cycle was repeated every 3 weeks. In the T93MP trial (17), Poor risk patients were randomized between four cycles of BEP every 3 weeks or cycles of cyclophosphamide (400mg/m2 on days 1-2), doxorubicin (35mg/m2 on days 1-2) and cisplatin (100 mg/m2 on day 3) and vinblastine (2.5 mg/m2/d) and bleomycin (25 mg/d) from days 1 to 5, alternatively. At the end of chemotherapy, the surgical resection of all residual masses was performed.

Patients with incomplete response were excluded from the current study: 24 from T93BP and 84 from T93MP. The study population thus consists of 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 news.

Parametric Mixture cure models

After treatment for metastatic NSGCT, patients in complete response or partial response with marker negative enter in a remission phase. Many of them will not relapse during follow-up. The other cases will present recurrences a few months or several years after treatment.

In classical survival analysis, it is assumed that all patients will present the event of interest if they are followed indefinitely. To relax this assumption Boag (19) proposed a parametric mixture cure model where he assumed that a fraction of patients (π with $0 \le \pi \le 1$) are cured of the disease, while the remaining patients will have recurrence. He assumed that the

time before recurrence in the second fraction of patients $(1-\pi)$ follows a log-normal distribution denoted by $F_R(t)$. The mathematical expression of the Boag model is

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

Using this methodology it is possible to identify prognostic factors for the cure rate and the hazard distribution (20,21).

Duration of post-therapeutic follow-up

Duration of post therapeutic follow-up can be defined using a two-step approach (4). In a first step, the parameters of the parametric cure model are estimated from the data. These parameters are then used to estimate the number of patients who will eventually relapse after the end of follow-up. Considering a population of 1000 patients, figure 1 represents the number of patients who present relapse after 7 years and the number of patients cured after treatment. Among the patients who recurred only a certain proportion will be treated with success in case of early detection. Let us consider $\upsilon; 0 \le \upsilon \le 1$ the probability that a patient whose relapse has been detected early is successfully treated. If N patients are followed-up for a total duration of $t_{\max}$ years, the total number of patients who will relapse after the end of follow-up who could have been successfully treated in case of early detection is:

$$\varepsilon(t_{\max}, N) = N \times \upsilon \times (1-\pi)(1-F_R(t_{\max})).$$

Statistical Considerations

Data on T93BP and T93MP were analyzed separately. For descriptive analysis, patients' characteristics were presented as frequency and median (range) respectively for categorical and continuous variables. Relapse Free Interval rates were estimated using Kaplan-Meier method and the Boag mixture cure model. The effects of covariates on the cure fraction were modeled with a logistic link which leads to the estimation of odds ratios. Statistical analysis was performed with STATA release 12 (StataCorps Tx.).

Results

T93BP example

The 246 patients from T93BP trial were aged from 16 to 59 years. The cancer was mostly localized in the testis (99%) and 109 (44%) had teratocarcinoma which was the most frequent histology subtype (table 2). Among these patients, 43 presented partial responses and 203 a complete response (clinical n= 92, pathologic n= 100, surgical n= 11). After a median follow-up of 53 months (95%CI = [51 – 58]), 12 patients died, and the five year overall survival rate was estimated as 93.8% (95%CI = [88.6 – 96.7]). During follow-up, 20 patients presented relapse and the relapse free survival was estimated as 95.1% and 93.8% and 92.1% at 6 months, 12 months and 5 years respectively.

Overall Population

Estimates from Kaplan-Meier and the Boag model are presented in figure 2. The estimated parameters of the model are shown in table 3. The cure rate was estimated as 91.3% (95%CI = [86.8 - 94.4]). Starting with a population of 1,000 patients, Figure 3 (left) represents the number of patients who relapse after the end of follow-up and who could have been successfully treated in case of early detection, according to the probability of success of the salvage treatment. For example if this probability is 80%, the number of patients who relapse after 5, 7 and 10 years who could have been treated with success in case of early detection are respectively 2, 1 and 0 on a cohort of 1,000 patients.

Prognostic Factors: Type of response

Due to the small number of events, only the association between type of response and cure rate was investigated (p=0.007). Patients with complete response were associated with a higher cure rate (93.7%; 95%CI = [89.2 – 96.4]) compared to patients with partial response (79.6%, 95%CI = [63.8 – 89.6]). A probability of success of salvage treatment equal to 80% is assumed for 1,000 patients presenting complete response at end of treatment. Then, the estimated delayed diagnosis cases were 2, 1 and 0 if follow-up stopped at 5 years, 7 years and 10 years (Figure 3 right side). In case of partial responses (n=1,000), the number of delayed case were 4, 2 and 1.

T93MP example

Clinical characteristics of the patients included in the T93MP trial are presented in table 2. They had comparable characteristics with T93BP: 16-62 age range, 76% of the sites in the testis and 42% of the histology was teratocarcinoma. Among these, 27 patients presented

partial responses and 79 complete response (clinical n= 5, pathologic n= 60, surgical n= 14). The median follow-up was 96 months (95%CI = [92 – 104]) and 20 patients died. The five year overall survival rate was estimated as 80.8% (95%CI = [71.9 – 87.2]). Finally, 33 relapses were observed and the relapse free survival rates were 72.3%, 71.3% and 70.0% at 2, 5 and 7 year respectively.

Overall Population

The estimated cure rate for the T93MP trial patients was 64.6% (95%CI = [52.2 - 75.2]), according to the overall model of table 3. Considering a probability of salvage treatment of 20% and 1,000 patients, the number of patients who relapse after 5, 7 and 10 years who could be treated with success in case of early detection can be estimated to 10, 7 and 5 (figure 4, left side).

Prognostic Factors

No significant association was found between response and cure rate (p=0.101). The IGCCCG classification was associated with cure rate (p=0.028). Patients classified as intermediate and good prognosis had a higher cure rate (75.5%, 95%CI = [60.5 – 86.1]) than those in poor IGCCCG class (52.6, 95%CI = [35.8 – 68.9]). Supposing a population of 1,000 patients in each group, figure 4 (right side) represents the number of delayed diagnosis according to different duration of post therapeutic follow-up and supposing a probability of salvage treatment of 20%. For patient with good to intermediate IGCCCG if follow-up was stopped at 5, 7 and 10 years, the estimated number of delayed cases were respectively 6, 4 and 3 patients. In the case of poor IGCCCG class they would have been respectively 14, 10 and 7.

Discussion

Four main reasons can be defined for patients' follow-up after treatment (12): detection of relapse, detection of second primary cancer, detection of late physical or physiological effects and knowledge improvement. The chances of achieving these objectives increase with more follow-up visits. However some logistical and financial issues are encountered in the case of too frequent visits and too long follow-up. Moreover, Van As et al. (12) have highlighted among others, the risks of developing several primary malignancies due to over exposition to radiological examination. The recommended follow-up schedules for testicular seminoma have not yet been validated (11) and there is no consensus on how many years this should be undertaken. Additionally, follow-up schedules take into account few individual patient characteristics.

The concept presented here permits an objective determination and an individualization of the duration of post-therapeutic follow-up according to the distribution of time before recurrence. The optimal duration of follow-up should be constructed in such a way as to be effective in terms of costs, burden on the patient and detection of relapse at an early stage. The example presented on NSGCT shows how the classical guidelines can be improved. Some patients could be obviously followed-up shorter than the standard recommendations. Moreover the length of follow-up of good prognosis patients can be tailored according to the type of response after treatment. Figure 3 shows that good prognosis patients with partial response should be followed-up for a longer period than those with complete response, whatever the decision threshold value. The individualization of the follow-up of poor prognosis patients can also be undertaken according to the IGCCCG status. For example, patients with good to intermediate IGCCCG status will be in surveillance for a shorter period.

The developed approach is very understandable and can be easily implemented in decision making applications for medical use. The threshold for follow-up interruption should be decided by expert consensus. The model can even be adapted using different distributions than log normal such as logit, weibull, gamma, etc (20,22,23).

The presented two trials were designed in the early of 90's and have long term follow-ups. One limitation of this example is the fact that they were based on the Institut Gustave Roussy prognostic system (18) and not on the IGCCCG classification (24). This later classification is the incorporated system in the TNM classification as prognostic factors to categorize patients into good, intermediate, or poor prognosis (25). These two trials started their recruitment in

1993 and 1994, before the development of the IGCCCG classification (published in 1997). Another limitation is the accuracy of the confidence intervals. These are large, due to the small number of observed events. This limitation should however be put into perspective. Similar problems exist for the recommendation performed by different societies concerning follow-up. Then, these are not updated yearly despite the fast evolution of the treatment's prognoses. For example; as more efficient therapeutic strategies are being highlighted (10) the standard of treatment is currently changing in the group defined as poor prognosis and this may lead to shorter surveillances. However, studies are ongoing for more parsimonious models and more general cases (26).

The concept proposed here could help clinicians to determine the duration of the post-therapeutic surveillance. Proposing personalized follow-up duration is just as important as is the decision of prescribing individualized treatment. We hope this concept will be applied in larger data bases for different cancer sites as the application of the methodology should permit important cost savings and significantly reduce the workload of the health providers.

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Tables

Table 1

Table 1: Recommended minimum follow-up schedule in advanced NSGCT (15)

	Year			
	1	**2**	**3-5**	**There After**
Clinical Marker	4 times	4 times	Twice / Year	Twice / Year
Chest X-Ray				
Abdo Scan	twice	Twice	As indicated	As indicated
Cest Ct-scan	As indicated	As indicated	As indicated	As indicated

Table 2

Table 2: Patients characteristics

Trial		T93BP n=246	T93MP n=106
Age[1]	years	28 (16-59)	28 (15-62)
Disease site			
	Testis	243 (98.78)	81 (76.42)
	Retroperitoneum	3 (1.22)	8 (7.55)
	Mediastinum	0 (0.00)	17 (16.04)
Histology			
	Pure seminoma	0 (0.00)	1 (0.94)
	Pure embryonal-cell carcinoma	63 (25.61)	18 (16.98)
	Teratocarcinoma	109 (44.31)	44 (41.51)
	Choriocarcinoma / other	18 (7.32)	11 (10.38)
	Other mixed	56 (22.76)	32 (30.19)
Metastatic sites			
	Lung	67 (27.35)	52 (49.52)
	Liver	4 (1.63)	11 (10.38)
	gastric	0 (0.00)	0 (0.00)
	Cerebral	0 (0.00)	1 (0.99)
	Pleural effusion	2 (0.81)	8 (7.55)
Serum tumor markers[1]			
	Alpha-fetoprotein, ng/mL	16 (0-693)	947 (0-54727)
	Human chorionic gonadotropin, U/L	4.5 (0-1,952)	1340 (0-1,150,000)
	Lactate dehydrogenase, U/L	423 (4-17,320)	838 (0-9,411)
IGCCCG prognostic classification			
	Good	240 (97.56)	10 (9.44)
	Intermediate	0 (0.00)	45 (42.45)
	Poor	6 (2.44)	51 (48.11)
Responses			
	Clinical complete response	92 (37.40)	5 (4.72)
	Pathologic complete response	100 (40.65)	60 (56.60)
	Surgical complete response	11 (4.47)	14 (13.21)
	Partial response	43 (17.48)	27 (25.47)

[1]*Data are median(min – max)*

Table 3

Table 3: Model results for T93BP and T93MP

	T93BP			T93MP		
	Estimator	Std error	P.value	Estimator	Std error	P.value
Overall population						
			Cure fraction (logistic link)			
Intercept	2.36	0.24	0.000	0.60	0.26	0.021
			Recurrence distribution (log normal)			
Intercept	-0.41	0.26	0.113	-0.21	0.44	0.639
Log std deviation	0.00	0.20	0.980	0.54	0.19	0.004

Table 4

Table 4: Results from the modeling according to cure rate for T93BP patients

	Estimator	Std error	P.value
Cure fraction (Logistic link)			
Intercept	1.36	0.40	0.001
Complete response	1.34	.50	0.007
Recurrence distribution (log normal)			
Intercept	-0.40	0.26	0.124
Log std deviation	-0.01	0.20	0.963

Table 5

Table 5: Results from the modeling according to IGCCCG class for T93MP patients

	Estimator	Std error	P.value
Cure fraction (Logistic link)			
Intercept	0.11	0.35	0.766
IGCCG good to moderate	1.02	0.46	0.028
Recurrence distribution (log normal)			
Intercept	-0.21	0.43	0.624
Log std deviation	0.54	0.19	0.004

Figures

Figure 1

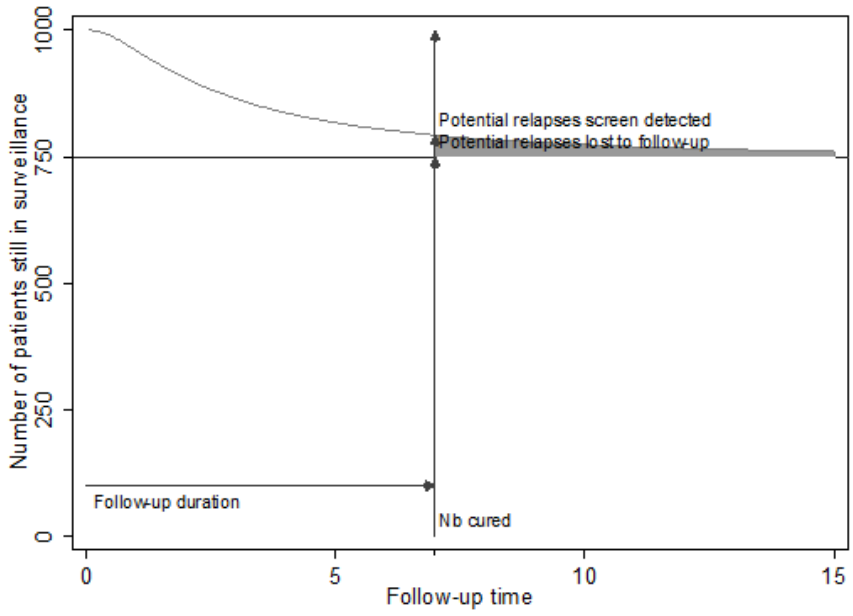

Figure 1: Illustration of the log normal cure model of Boag with 1,000 patients followed for 7 years

Figure 2

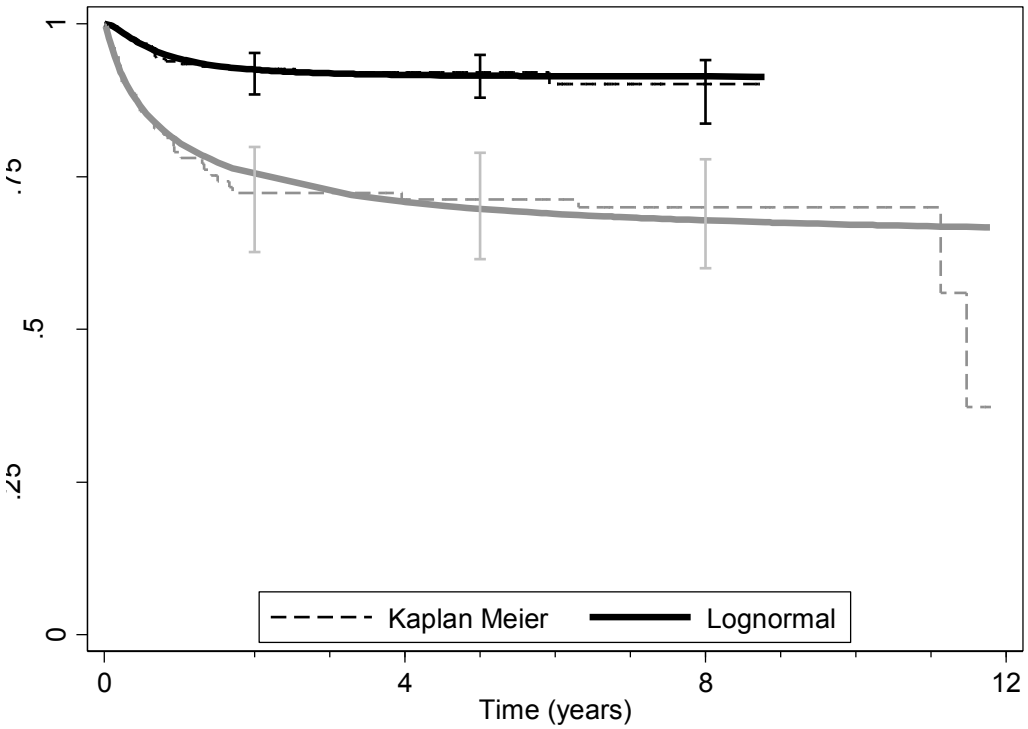

Figure 2: Kaplan-Meier and modeled survival function estimates for the T93BP (black) and T93MP (gray) trials

Figure 3

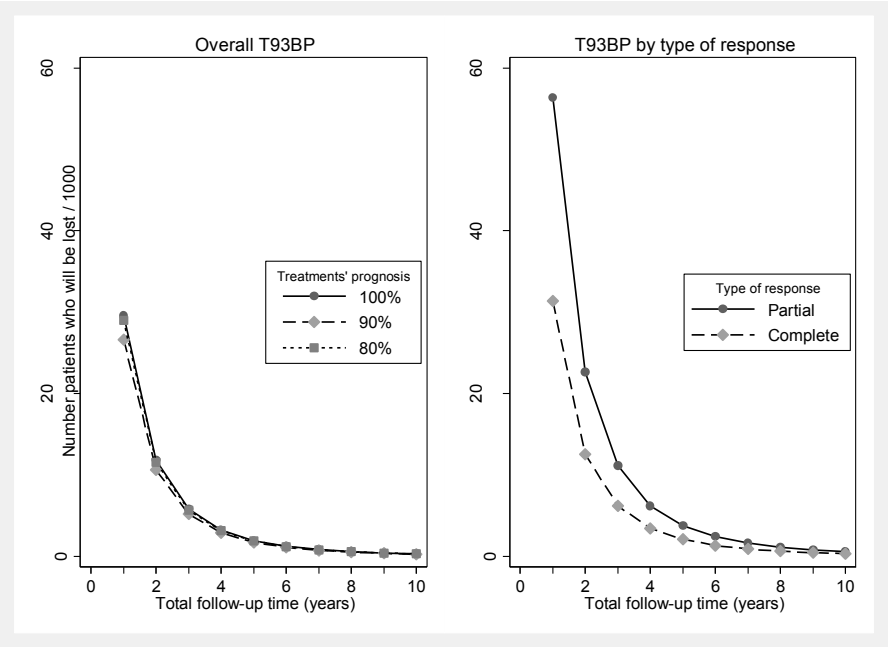

Figure 3: Number of lost T93BP patients over 1,000 according to the total follow-up time for different salvage treatment prognostics and according to type of response with salvage treatment prognostic of 80%.

Figure 4

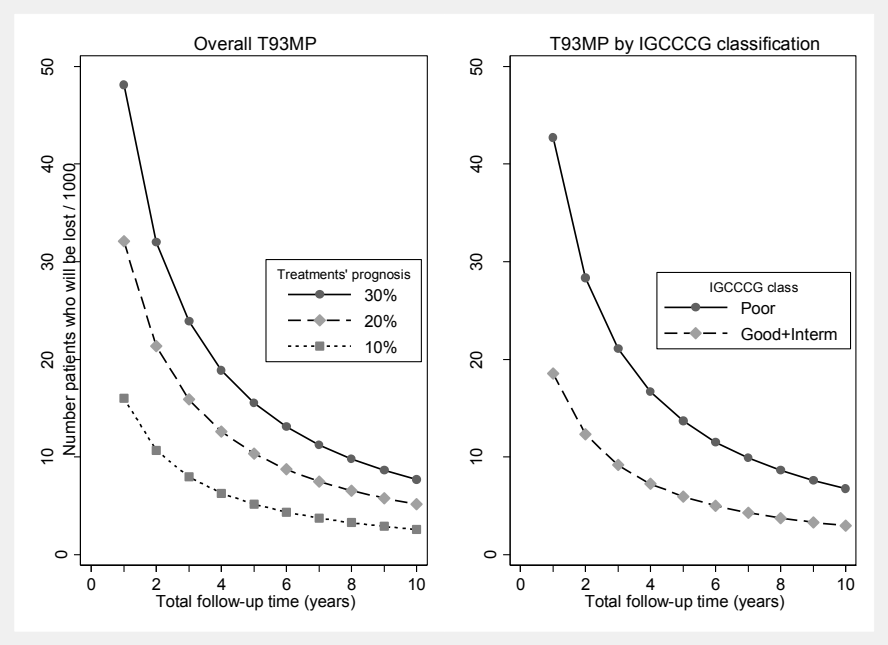

Figure 4: Number of lost T93MP patients over 1,000 according to the total follow-up time for different salvage treatment prognostics and according to IGCCCG class with salvage treatment prognostic of 80%.

II.5 Discussion

La méthodologie proposée par Mould *et al.* [36] est un outil évident d'aide à la décision. Elle est facile à assimiler par les praticiens. Cependant, cette approche ne permet de prendre en compte qu'un seul événement. Les malades en phase de rémission sont généralement à risque de plusieurs types de récidives : récidives locales ou régionales, métastases à distance, seconds cancers primaires, etc. Les distributions des risques de récidive en fonction des types d'événements sont aussi différentes et différemment influencées par les facteurs pronostiques. Les patients ne présentent pas les mêmes probabilités de rechute selon les différents types de récidive. Les connaissances médicales ne permettent pas non plus de prendre en charge les différents types de récidives avec les mêmes pronostics de guérison.

Les conditions d'application du modèle de Boag [56] ne permettent pas de modéliser la survie sans récidive dans le cas où plusieurs types d'événements distincts sont observés. L'approche proposée dans ce cas utilise une modélisation de risques compétitifs. En effet, étant donné que l'objectif est de détecter le premier événement, l'apparition d'une récidive empêche celle des autres comme premier événement. L'approche par les risques compétitifs est alors justifiée.

Jeong et Fine [72] ont proposé une approche directe de modélisation de l'incidence cumulée dans le cas de risques compétitifs. Cette approche présente plusieurs avantages :

- elle permet l'estimation de la distribution d'un événement de type spécifique en présence de concurrence ;
- elle ne nécessite pas l'estimation additionnelle de taux de guérison par un modèle de mélange ;
- elle présente un modèle plus parcimonieux ;
- les paramètres estimés sont directement interprétables par rapport à l'incidence cumulée.

III Approche par les risques compétitifs

III.1 Objectifs

Dans cette section, la stratégie de Mould *et al.* [36] est reproduite et adaptée à la modélisation des délais avant récidive dans le cas de plusieurs événements. Le modèle paramétrique d'estimation en présence de risques compétitifs de Jeong et Fine [72] est présenté. Ce modèle sera ensuite utilisé pour définir une méthodologie de détermination de la durée de survie en fonction des types de rechute.

III.2 L'approche directe de Jeong et Fine

Soit une population à risque de K événements concurrents. La fonction d'incidence cumulée $F_k(t)$, $k = 1, \ldots, K$, est définie comme la probabilité que l'événement de type k survienne avant le temps t en présence des autres évènements. L'approche directe de Jeong et Fine [72] pour la modélisation des durées de suivi à risques compétitifs consiste à modéliser les incidences cumulées par des distributions de lois impropres. Les $F_k(t)$ sont alors définis tels que $F_k(\infty) < 1$.

Pour une fonction d'incidence cumulée de distribution connue F_k avec $F_k(\infty) < 1$, la fonction de risque instantané est obtenue en effectuant la transformation suivante :

$$\lambda_k(t) = \frac{\mathrm{d}F_k(t)/\mathrm{d}t}{1 - F_k(t)}.$$

La fonction de répartition globale associée au premier événement est donc :

$$F(t) = \sum_{k=1}^{K} F_k(t).$$

La fonction de survie sans événement est par suite :

$$S(t) = 1 - F(t) = 1 - \sum_{k=1}^{K} F_k(t).$$

Jeong et Fine [72] ont proposé d'utiliser la distribution de Gompertz [73] pour modéliser la fonction d'incidence cumulée associée à un événement. La fonction d'incidence

cumulée associée à l'événement de type k est :

$$F_k(t;\Psi_k) = 1 - \exp\left[\frac{\beta_k}{\alpha_k}\{1-\exp(\alpha_k t)\}\right] \tag{II.4}$$

avec $\Psi_k = (\alpha_k, \beta_k) \in \mathrm{R}^* \times \mathrm{R}^+$.

Le modèle de Gompertz est traditionnellement utilisé en analyse de survie dans la biologie du vieillissement. Dans ce cas, le paramètre α_k est appelé *coefficient du taux de mortalité âge-dépendant* tandis que le paramètre β_k est appelé *coefficient du taux de mortalité âge-indépendant* [74]. Ces modèles sont aussi largement utilisés en démographie où ils permettent d'estimer les durées de vie des populations [75].

La fonction de densité est obtenue en dérivant la fonction d'incidence cumulée par rapport au temps.

$$f_k(t;\Psi_k) = \frac{\partial F_k(t;\Psi_k)}{\partial t} = \beta_k \exp(\alpha_k t + \frac{\beta_k}{\alpha_k}\{1-\exp(\alpha_k t)\}). \tag{II.5}$$

La fonction de risque instantané associée à l'événement de type k est ensuite obtenue comme suit :

$$\lambda_k(t;\Psi_k) = \frac{f_k(t;\Psi_k)}{1-F_k(t;\Psi_k)} = \beta_k \exp(\alpha_k t). \tag{II.6}$$

Enfin, la fonction de risque cumulé s'obtient immédiatement à partir de celle des risques instantanés.

$$\Lambda_k(t;\Psi_k) = \int_0^t \lambda_k(u;\Psi_k)\,\mathrm{d}u = -\frac{\beta_k}{\alpha_k}(1-\exp(\alpha_k t)). \tag{II.7}$$

Lorsque $\alpha_k < 0, \lim_{t\to+\infty} F_k(t) < 1$, la distribution de Gompertz est impropre. $p_k = F_k(\infty)$ est une asymptote horizontale de l'incidence cumulée avec $0 < p_k < 1$. Dans ce cas, la probabilité de ne pas observer de rechute de type k est estimée par

$$\pi_k = \lim_{t\to+\infty}(1-F_k(t)) = 1 - p_k = \exp(\beta_k/\alpha_k). \tag{II.8}$$

Par suite, on a $0 < \pi_k < 1$.

Dans la figure II.3, en prenant, à titre d'exemple, en colonne α = -0,50 ; -0,10 et -0,01 respectivement et en ligne β = 0,50 ; 0,10 et 0,01 respectivement, les courbes des fonctions d'incidence cumulée atteignent leurs plateaux à $1-\pi = 1-\exp(\frac{\beta}{\alpha})$, qui sont

toujours inférieurs à l'unité, ce qui donne des lois impropres.

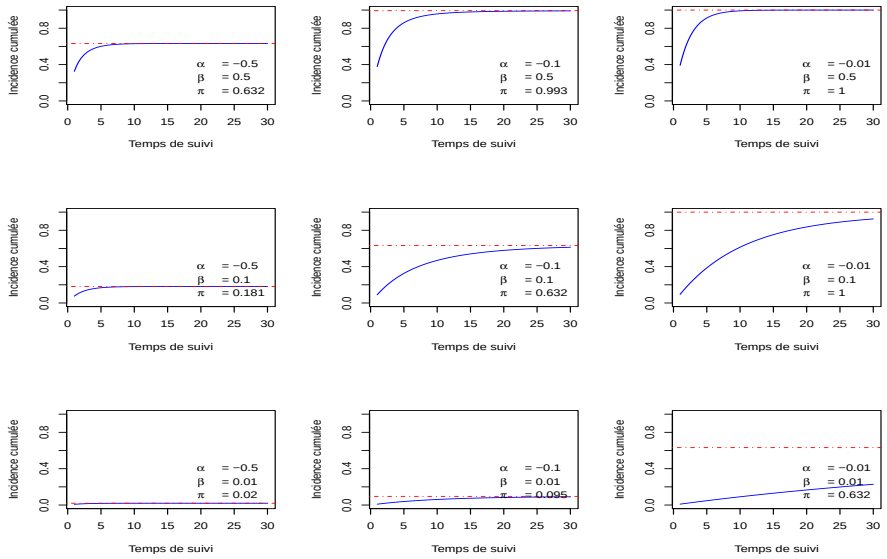

FIGURE II.3 – Incidences cumulées modélisées avec des distributions de Gompertz

Il faut cependant noter que si les F_k sont les fonctions de répartitions des risques pour chaque événement k, la fonction de répartition globale

$$P\left[T \leq t, \Psi_1, \ldots, \Psi_K\right] = K - \sum_{k=1}^{K} \exp\left[\frac{\beta_k}{\alpha_k}\{1 - e^{\alpha_k t}\}\right]$$

ne suit pas une distribution de probabilité classique [76]. Il n'est pas possible de la modéliser directement sans passer par les incidences cumulées spécifiques. La proportion de patients qui auront au moins un événement est alors :

$$1 - \pi = \sum_{k=1}^{K}(1 - \pi_k) = K - \sum_{k=1}^{K}\exp(\beta_k/\alpha_k), \tag{II.9}$$

alors que la proportion de patients qui n'auront aucun événement est :

$$\pi = 1 - K + \sum_{k=1}^{K}\exp(\beta_k/\alpha_k). \tag{II.10}$$

Jeong et Fine [77] ont ensuite proposé l'incorporation de deux catégories de para-

mètres pour prendre en compte les facteurs pronostiques. Ils considèrent un coefficient de régression γ_k ainsi qu'un paramètre de flexibilité τ_k. Le modèle de régression de Jeong et Fine donne par suite :

$$F_k(t, Z) = 1 - \{1 + \tau_k \exp({}^t\gamma_k Z)\Lambda_k(t)\}^{-\frac{1}{\tau_k}} \tag{II.11}$$

où $\Lambda_k(t) = -\frac{\beta_k}{\alpha_k}(1 - e^{\alpha_k t})$ correspond à la fonction de risque cumulé lorsqu'on utilise la distribution de Gompertz sans facteurs pronostiques présentée dans l'équation II.7.

En notant $\Phi_k = (\alpha_k, \beta_k, \tau_k, {}^t\gamma_k)$ le vecteur des paramètres, la fonction d'incidence cumulée s'écrit en fonction des facteurs pronostiques comme suit :

$$F_k(t, \Phi_k, Z) = 1 - \{1 - \tau_k \frac{\beta_k}{\alpha_k} \exp({}^t\gamma_k Z)(1 - e^{\alpha_k t})\}^{-\frac{1}{\tau_k}}. \tag{II.12}$$

La probabilité de ne pas présenter d'événement de type k s'exprime alors comme suit :

$$\pi_k = \lim_{t \to +\infty}(1 - F_k(t, \Phi_k, Z)) = \{1 - \tau_k \frac{\beta_k}{\alpha_k} exp({}^t\gamma_k Z)\}^{-\frac{1}{\tau_k}}. \tag{II.13}$$

L'effet des facteurs pronostiques est assez difficile à interpréter en l'état. Cependant, en attribuant certaines valeurs spécifiques au paramètre τ_k, il est possible de retrouver des effets classiques des coefficients de régression.

La fonction d'incidence cumulée du modèle de Jeong et Fine lorsque $\tau_k \to 0$ est égale à

$$F_K^0(t, \Phi_k^0) = 1 - \exp(\frac{\beta_k}{\alpha_k} e^{{}^t\gamma_k Z}(1 - e^{\alpha_k t})). \tag{II.14}$$

Dans ce cas, le modèle répond aux conditions d'un modèle à risques proportionnels. Il y a par contre côtes proportionnelles lorsque $\tau_k = 1$. Dans ce cas, la fonction d'incidence cumulée du modèle de Jeong et Fine est égale à

$$F_K^1(t, \Phi_k^1) = 1 - \{1 - \frac{\beta_k}{\alpha_k} e^{{}^t\gamma_k Z}(1 - e^{\alpha_k t})\}^{-1}. \tag{II.15}$$

III.3 La fonction de perte

La *fonction de perte* est définie comme étant la probabilité pour un patient de rechuter après un temps donné (la durée de sa surveillance post-thérapeutique), alors qu'il aurait été traité avec succès si sa récidive avait été détectée de manière précoce.

Considérons des patients en phase de rémission après un traitement curatif d'un cancer donné. Ces patients sont considérés à risque de K événements (qui peuvent être des récidives locales, régionales, métastatiques, etc.). Soient $\nu_k, 0 \leq \nu_k \leq 1$ la probabilité d'être traité avec succès en cas de détection précoce d'un événement de type k.

La fonction d'incidence cumulée $F_k(t)$ représente la probabilité d'observer un événement de type k avant un temps t donné. Cette probabilité est estimée à l'aide du modèle de Jeong et Fine. Par suite, la proportion des patients qui ne connaîtront jamais un événement de type k est donnée par π_k tel que :

$$\pi_k = \lim_{t \to +\infty} F_k(t).$$

La quantité $1 - \pi_k - F_k(t)$ représente la proportion de patients qui connaîtront un événement de type k après la date t. Si la surveillance est interrompue à partir de cette date, ces patients auront une récidive de type k qui ne sera pas détectée de façon précoce. De plus, une part ν_k de ces récidives non détectées aurait pu être traitée avec succès.

La perte engendrée en décidant d'interrompre la surveillance après un délai t pour une récidive de type k est par conséquent la quantité suivante :

$$\varepsilon_k(t; \Psi_k) = \nu_k \times [1 - \pi_k - F_k(t; \Psi_k)]\,. \tag{II.16}$$

La perte globale est la perte engendrée en décidant d'interrompre la surveillance après un délai t, en prenant en compte tous les types d'événements. Elle s'obtient en sommant les fonctions de pertes de chaque type d'événement. La fonction de perte est définie comme la probabilité d'avoir un événement qui aurait pu être traité avec succès après la date t :

$$\varepsilon(t; \Psi) = \sum_{k=1}^{K} \nu_k \times [1 - \pi_k - F_k(t; \Psi_k)]\,. \tag{II.17}$$

Ainsi, si N patients entrent en phase post-thérapeutique, le nombre de patients qui rechuteront après la fin du suivi et qui auraient pu être traités avec succès est obtenu par $N \times \varepsilon(t^*, \Phi)$ où t^* est la durée de suivi.

III.4 Article : Durée de surveillance en présence de risques compétitifs.

L'article suivant, publié dans la revue ***Medical Decision Making*** présente une méthode permettant de déterminer la durée de suivi pour un patient en phase de rémission de son un cancer. Elle permet de considérer spécifiquement les différents types d'événements auxquels ce patient pourrait être à risque. De plus, elle permet de prendre en compte les facteurs pronostiques afin d'individualiser le rythme de suivi.

ORIGINAL ARTICLE

Determining the Length of Posttherapeutic Follow-up for Cancer Patients Using Competing Risks Modeling

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Background/Objective. *After a curative treatment for cancer, patients enter into a posttherapeutic surveillance phase. This phase aims to detect relapses as soon as possible to improve the outcome. Mould and others predicted with a simple formula, using a parametric mixture cure model, how long early-stage breast cancer patients should be followed after treatment. However, patients in posttherapeutic surveillance phase are at risk of different events types with different responses according to their prognostic factors and different probabilities to be cured. This paper presents an adaptation of the method proposed by Mould and others, taking into account competing risks. Our loss function estimates, when follow-up is stopped at a given time, the proportion of patients who will fail after this time and who could have been treated successfully.* ***Method.*** *We use the direct approach for cumulative incidence modeling in the presence of competing risks with an improper Gompertz probability distribution as proposed by Jeong and Fine. Prognostic factors can be taken into account, leading to a proportional hazards model. In a second step, the estimates of the Gompertz model are combined with the probability for a patient to be treated successfully in case of relapse for each event type. The method is applied to 2 examples, a numeric fictive example and a real data set on soft tissue sarcoma.* ***Results and Conclusion.*** *The model presented is a good tool for decision making to determine the total length of posttherapeutic surveillance. It can be applied to all cancers regardless of the localizations.* ***Key words:*** *posttherapeutic follow-up; competing risks modeling; Gompertz distribution; cancer.* ***(Med Decis Making 2014;34:168–179)***

At the end of primary treatment for cancer, patients enter into a phase of posttherapeutic surveillance. This phase is designed to follow patients regularly in order to detect relapse at an early enough stage to apply therapeutic interventions with curative intent. Considering these objectives, different groups such as the American Society of Clinical Oncology (ASCO), the European Society of Medical Oncology (ESMO), and other medical societies have proposed guidelines for the follow-up of breast,[1,2] lung,[3] and colorectal cancers,[4] among others. These different guidelines propose regular visits that include clinical examinations, imagery, and/or biological markers. For example, for soft tissue sarcoma, ASCO and ESMO have suggested an examination schedule of every 3–6 months for 3 years and then every 6–12 months for 2 years followed by an indefinite period of annual follow-up with chest radiography.[5–7]

These predefined schedules have the advantage of being easy to apply in the wards, but they do not necessarily allow the detection of events in an optimal manner. In fact, these surveillance calendars do not take into account that the incidence of recurrences depends on the time since the primary treatment.

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Also, prognostic factors are not used to identify the subpopulations that are more or less at risk of relapse over time. Usually, all patients are followed with the same protocol; however, the recurrence times may differ according to some main factors, so the schedule applicable to one patient may not be suitable for another one.

The number of patients entering a posttherapeutic phase is increasing, and some types of cancer, such as breast cancer, have a very good prognosis, which can be related to widely advertised screening programs and improvements in adjuvant treatments. As the patient follow-up workload increases every year, so do the associated financial resources. For these reasons, different methods have been proposed in the literature to individualize patient follow-up according to the risk of relapse. Wheeler and others[8] used the data of 416 patients to estimate the annual recurrence hazard rates. They concluded that the ideal follow-up should be sensitive to the likelihood of relapse. Kent and others[9] proposed a nonlinear optimization approach to schedule follow-up cystoscopies to detect recurrence of bladder cancer. The authors proposed longer intervals between visits for low-risk patients and shorter intervals between visits for high-risk patients. Finally, Filleron and others[10] developed a 2-stage strategy. Prognostic factors associated with time to failure were identified, and then visits were planned using quantiles of the cumulative incidence or the cumulative risk function. These different methods permit clinicians to plan follow-up visits, but the duration of posttherapeutic surveillance is hardly addressed in the literature. Certain patients will never experience a relapse and will nevertheless be followed during a long period. The duration of posttherapeutic follow-up is of prime importance in the management of follow-up care and financial resources.

Ideally, the surveillance phase should last until the patient is considered ''cured,'' that is, no longer at risk of relapse. This delay can be estimated through relative survival techniques.[11,12] Tai and others[13] provided an approach based on the assumption of a log-normal distribution to establish the threshold time required to estimate a statistical cure rate. These threshold times vary greatly depending on the cancer site, ranging from 2.6 years for pancreatic cancer to 36.2 years for breast cancer (for thyroid cancer, the threshold time is estimated to 134.1 years).[13] Mould and others[14] proposed a simple formula as an aid in predicting the duration of follow-up after treatment for patients with early-stage breast cancer. They used the parametric Boag[15] model, based on log-normal modeling, to estimate the proportion of loco-regional recurrences that are expected to occur after the end of posttherapeutic follow-up and that could have been potentially cured. This method, however, takes into account only one type of event. We propose here an adaptation of this method to take into account several events with different probabilities of cure. First, the background and the method proposed by Mould are presented. Next, we present an extension of this method for competing risks. Then 2 applications are presented in the fourth section, and finally the method is discussed.

BACKGROUND

Patients in the posttherapeutic surveillance phase after treatment for cancer such as early breast cancer are at risk of local recurrence (LR). The main objective of this surveillance is to detect the occurrence of this event at an early stage in order to propose a potential curative treatment. As some of the patients will not relapse at all, the recurrence-free survival must be estimated through a ''cure model,'' that is, a survival model comprising a fraction of the population who will never experience the event of interest.

Boag[15] has proposed a 2-component mixture model for the analysis of survival in the presence of cure. This model assumes that a fraction $\pi(0 \leq \pi \leq 1)$ of patients will never have LR and a proportion $(1 - \pi)$ will experience LR. π is called *cure fraction*. The model hypothesizes that the failure times associated with LR follow a log-normal distribution. The local relapse-free survival function (i.e., the probability of local relapse-free survival to t) is given by

$$S_{LR}(t, \pi, \mu, \sigma) = \pi + (1 - \pi)\{1 - F^*_{LR}(t, \mu, \sigma)\},$$

where F^*_{LR} is the cumulative distribution function of a log-normal distribution with mean μ and standard error σ.

During posttherapeutic follow-up, a recurrence can occur several years after the end of the treatment, and the cost of regular follow-up examinations will be important. Using a 2-step method, Mould and others proposed to reduce the length of posttherapeutic follow-up for this patient population in order to detect all but a small number of patients who can be successfully treated for their recurrence.[14] In a first step, using the mixture cure model proposed by Boag,[15] they studied the delay until the first LR.[16]

In a second step, Mould and others assume a treatment success probability after early detection of LR, denoted by ν. In this case, it is assumed that all relapses during the follow-up period are screen detected.

So, the population that enters a posttherapeutic phase can be subdivided into 3 subgroups:

1. A proportion π of patients who will never relapse (the cure fraction)
2. A proportion $\nu \times (1-\pi)$ of patients who will relapse and who will be successfully treated for their relapse
3. A proportion $(1-\nu) \times (1-\pi)$ of patients who will relapse and who will not be successfully treated for their relapse

The authors proposed to reduce the length of follow-up as much as possible without significantly reducing the proportion of patients of the second subgroup.

The optimal length of follow-up, denoted t_{opt}, is determined in such a way that the proportion of patients who will relapse after the end of surveillance and who could be successfully treated if diagnosed is smaller than a given value ε.

$$\nu \times (1-\pi) \times \left\{1 - F^*_{LR}(t_{opt}, \mu, \sigma)\right\} \leq \varepsilon,$$

then,

$$\nu \times \left\{S_{LR}(t_{opt}, \pi, \mu, \sigma) - \pi\right\} \leq \varepsilon.$$

If N patients enter a posttherapeutic follow-up, the expected number of relapses that could have been successfully treated after the end of follow-up is given by

$$N_{LR}(t_{opt}) = N \times \nu \times \left\{S_{LR}(t_{opt}, \pi, \mu, \sigma) - \pi\right\}.$$

The method was applied to real data for early breast cancer patients treated between 1981 and 1990 and followed for 10 years.[16] Mould and others have found that if the follow-up was conducted for 4 years, the proportion of the patients who would relapse after the end of the surveillance and who could have been successfully cured if their recurrence was detected is estimated as 0.12%. Their estimated model had a mean of 0.34 and a standard deviation of 0.83. The time value $T = 4$ years provides a tail area of 10%. This means that 10% of the fraction $(1-\pi)$ experiences a delay in being diagnosed with an LR. With given $\pi = 0.85$ and $\nu = 0.80$, if follow-up was stopped after 4 years, for a population of 1000 patients, the number of patients who will relapse after the end of surveillance and who could be successfully treated if determined is

$$N_{LR}(4) = 1,000 \times 0.80 \times$$
$$[\{0.85 + (1-0.85) \times (1-0.90)\} - 0.85] = 12.$$

The follow-up could be shortened from 10 to 4 years, tolerating the loss of 12 patients among 1000 who could have been successfully treated if they had been followed for their entire lifetime. If the follow-up is conducted for 8 years, the relapse-free survival will be 5% and the number of patients lost among 1000 who could have been successfully treated if diagnosed will be 6.

The method proposed by Mould and others uses the Boag model, which assumes that the failure times follow a log-normal distribution. Other distributions such as Weibull or log-logistic can be used.[17] A cure rate can be estimated using a modified Gompertz distribution, which would result in an improper distribution (i.e., $\lim_{t\to\infty} S(t) > 0$).[18]

The method presented above permits the reduction of the length of follow-up schedules according to a unique type of relapse. However, during the posttherapeutic follow-up, cancer patients are at risk of multiple types of relapses: loco-regional recurrence (event 1), contralateral localization (event 2), and distant metastasis (event 3). The cumulative incidence functions associated with these different events, that is, the probabilities of experiencing a given type of event before a given delay, do not have the same distributions and may not be influenced by the same prognostic factors. Figure 1 is the schematic diagram for different first issues in the case of breast cancer. The probabilities for experiencing the 3 event types as first event are, respectively, p_k $(k = 1, 2, 3)$. As the probability to be cured after an event depends on the event type, it seems logical to adapt the method proposed by Mould and others with competing risks modeling. The modified Gompertz distribution of Gieser and others[18] has therefore been extended to competing risk modeling.

METHOD

Notations for Competing Risks Modeling

The different types of first relapses are considered to be mutually exclusive, competing events. Let us consider the following notations:

- K is the number of competing events.
- T_i is the observed time between the end of treatment of a patient i and the occurrence of the first event or the date of loss to follow-up.
- δ_{ki} is the indicator of the realization of event type k as first event, $k = 0, 1, \ldots, K$ for patient i. $\delta_{ki} = 1$ $(k = 1, 2, \ldots, K)$ indicates that the individual i had event type k as first event during his surveillance. $\delta_{0i} = 1$ indicates that the individual i did not have any event during his surveillance

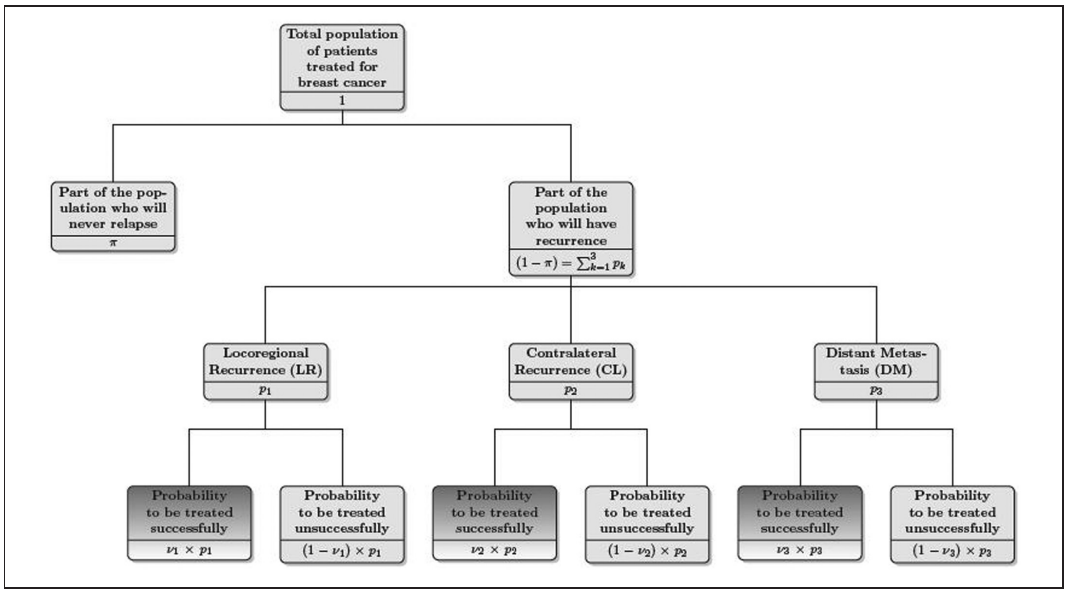

Figure 1 Schematic diagram for different issues in the case of 3 competing events and a cure fraction. The objective of the follow-up is to detect the maximum of patients in the shaded boxes.

and was censored. Thus, the following relationship is verified where I is the set of the individuals:

$$\forall\, i \in I;\ \sum_{k=0}^{K} \delta_{ki} = 1.$$

The cumulative incidence function (CIF),[19] denoted $F_k(k = 1; 2; \ldots; K)$, is the probability that an event of type k occurred before time t. The mathematical formulation of this function is given by

$$F_k(t) = P[T \le t, \delta_k = 1].$$

If $S(t)$ is defined as the relapse-free survival function, with $S(t) = P[T > t]$, then

$$\sum_{k=1}^{K} F_k(t) = 1 - S(t).$$

The Direct Approach for Competing Risks Modeling

The general form of the model. Jeong and Fine[20] proposed a method to parameterize directly the CIF associated with each type of first event. Each CIF is modeled through its own probability distribution. As the probability of each event is less than 1, it is necessary to use improper distributions.

The CIF associated with an event type k, modeled with a Gompertz distribution, is defined by

$$F_k(t, \alpha_k, \beta_k) = 1 - \exp\left\{\frac{\beta_k}{\alpha_k}\left(1 - e^{\alpha_k t}\right)\right\},$$

where α_k is the shape parameter of the distribution and β_k the scale parameter. The Gompertz distribution is improper when $\alpha_k < 0$ and $\beta_k > 0$. Then

$$\lim_{t\to\infty} F_k(t, \alpha_k, \beta_k) = 1 - \exp(\beta_k/\alpha_k) = p_k < 1,$$

where p_k is the probability of having event of type k as first event.

The proportion π of individuals who will never experience an event is given by

$$\pi = 1 - \sum_{k=1}^{K} p_k = 1 - K + \sum_{k=1}^{K} e^{\frac{\beta_k}{\alpha_k}}.$$

The use of covariates. Let us denote Z the vector of covariates and γ_k the vector of regression parameters associated with event type k. γ_k' is the transpose of γ_k. Jeong and Fine[21] proposed a regression model that can handle the effect of covariates. Their model

includes a parameter τ_k that allows flexibility to avoid making assumptions about the effect of covariates:

$$F_k(t,\alpha_k,\beta_k,\tau_k,\gamma_k,Z)=1-\left\{1-\tau_k\frac{\beta_k}{\alpha_k}e^{\gamma_k'Z}\left(1-e^{\alpha_k t}\right)\right\}^{-\frac{1}{\tau_k}}.$$

For numerical simplification purposes, we retain only the model assuming proportional hazards. We have a proportional hazards model when $\tau_k \to 0$. In this case, the CIF is

$$F_k^{PH}(t,\alpha_k,\beta_k,\gamma_k,Z)=1-\exp\left\{\frac{\beta_k}{\alpha_k}e^{\gamma_k'Z}\left(1-e^{\alpha_k t}\right)\right\}.$$

The likelihood function. The parameters (α,β,γ) are estimated by likelihood maximization. The likelihood function is defined by

$$L(\alpha,\beta,\gamma|t,Z)=\prod_{i\in I}\left\{\prod_{k=1}^{K}\left[f_k(t_i,\alpha_k,\beta_k,\gamma_k,Z_i)\right]^{\delta_{ki}}\times\left[1-\sum_{k=1}^{K}F_k(t_i,\alpha_k,\beta_k,\gamma_k,Z_i)\right]^{\delta_{0i}}\right\},$$

where $f_k(t,\alpha_k,\beta_k,\gamma_k,Z)$ is the probability density function associated with $F_k(t,\alpha_k,\beta_k,\gamma_k,Z)$, and

$$(\alpha,\beta,\gamma)=\begin{bmatrix}\alpha_1 & \beta_1 & \gamma_1\\ \vdots & \vdots & \vdots\\ \alpha_K & \beta_K & \gamma_K\end{bmatrix}.$$

The Loss Function

With the direct approach of Jeong and Fine, one can estimate separately the cumulative incidence of each competing event for a given time. An important issue for the clinician is the probability of relapse after a given follow-up time. He or she may decide to discontinue the surveillance if this probability is less than a threshold value. Because the prognoses of the different event types are different, the method proposed by Mould and others can be applied to each event type separately. A loss function can be estimated for each event type by weighting its probability with the probability of being successfully treated if it is diagnosed early.

The overall loss function estimates, for a surveillance time t, the probability of having a recurrence after t that could have been successfully treated if it had been detected earlier.

The probability for a patient to experience an event of type k as first event is estimated by $p_k=\lim_{t\to\infty}F_k(t)$. The probability for a patient to have already experienced an event of type k at time t is estimated by $F_k(t)$. So $p_k-F_k(t)$ is the probability for a patient to experience an event of type k after time t. As in Mould and others,[14] if we tolerate a given loss ε, we can determine the optimal follow-up t_{opt}.

Let us consider $\nu_k;k=1;\ldots;K$ the probability of success of the treatment after early detection of an event of type k. We define the loss function associated with event type k as the probability for a patient to have an event of type k after time t, corresponding to the last follow-up visit, which could be treated successfully if diagnosed. The expression of the loss function associated with event type k is

$$\varepsilon_k(t)=\nu_k(p_k-F_k(t)).$$

The overall loss function is defined as the probability for a patient to have an event after time t, corresponding to the date of the end of follow-up, which could have been treated successfully if diagnosed. The expression of the overall loss function is

$$\varepsilon(t)=\sum_{k=1}^{K}\varepsilon_k=\sum_{k=1}^{K}\nu_k(p_k-F_k(t)).$$

If the follow-up is stopped at time t, a proportion $\varepsilon(t)$ of potentially curable patients will be lost. The Jeong and Fine models, with and without covariates, the loss function, and its covariance matrix have been programmed with R software.[22]

APPLICATION

Illustration With Numerical Example

Let us consider patients who enter a posttherapeutic follow-up after treatment for breast cancer. We consider they are at risk of 3 types of events: locoregional recurrence (LRR), contralateral localization (CL), and distant metastasis (DM). The parameters (α_k,β_k) used for this example are presented in Table 1. The cumulative incidence estimates at 5 and 10 years used to determine these parameters were inspired by the literature in a population of patients at a high risk of relapse.[23]

The model of Jeong and Fine gives directly the cumulative incidence for any specific type of event for a given delay. The values of the CIF at 10 years are, for example,

$$F_k(10,\alpha_k,\beta_k)=1-\exp\left[\frac{\beta_k}{\alpha_k}(1-\exp(10\times\alpha_k))\right].$$

Table 1 Parameters Used for the Example.

	Loco-regional Relapse (%)	Contralateral Localization (%)	Distant Metastasis (%)
$\psi_k = (\alpha_k, \beta_k)$	(–0.300; 0.050)	(–0.140; 0.016)	(–0.160; 0.080)
$F_k(5\ years)$	12.1	5.6	24.1
$F_k(10\ years)$	14.7	8.3	32.9
$F_k(\infty)$	15.4	10.8	39.3
ν_k	80.0	90.0	05.0

The probability for a patient to experience an LRR as first event before 10 years is 14.7%. The probability to experience an LRR as first event (without considering the delay) corresponds to the asymptote value ($p_1 = 1 - \exp(\beta_1/\alpha_1)$), which is equal to 15.4%. In a similar manner, the probabilities corresponding to CL and DM are 10.8% and 39.4%, respectively. So 34.5% of the patients will never experience any relapse. This correspond to the cure rate π. The parametric cumulative incidences for each event type (LRR, CL, and DM) are presented in Figure 2A.

So the probability of having a loco-regional relapse as first event after 10 years is 0.7% ($p_1 - F_1(10) = 0.154 - 0.147$). If the follow-up is suspended after these 10 years, 0.7% of the LRRs will not be diagnosed early enough to provide good responses to a curative treatment.

Let us consider the treatment success probability for an LRR as ν_1 = 80%. Then, if the surveillance is stopped after 10 years, 0.56% of the population will have an LRR after the end of the surveillance that could have been treated if correctly diagnosed. This corresponds to the value of the loss function specific to LRR for 10 years. The different specific loss functions are calculated with treatment success probabilities of 90% and 5%, respectively, for CL and DM. The overall loss function corresponds to the sum of the different specific loss functions. Figure 2B gives estimates of the number of patients who will relapse after the end of surveillance and whose recurrence could have been treated successfully for a set of 1000 patients in posttherapeutic phase, according to our example. The results are presented for each specific relapse type and overall.

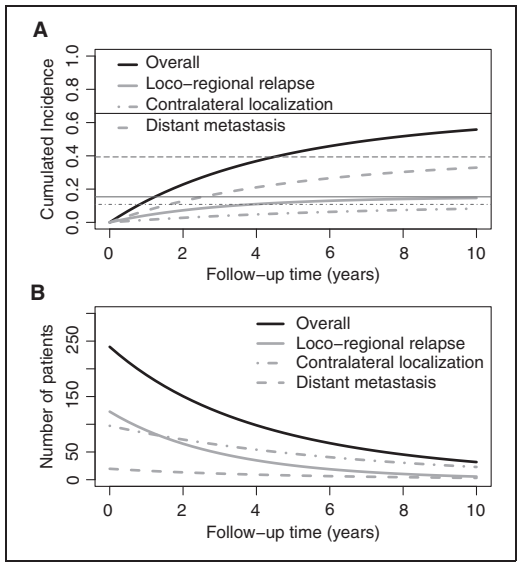

Figure 2 (A) Cumulative incidence function for each event type and overall. Horizontal lines represent the values of the asymptotes. (B) Number of patients relapsing after the end of follow-up who could be treated successfully.

Application to Real Data

The method described above has been used to compute the loss function of a population of patients treated for soft tissue sarcoma. The soft tissue sarcomas are a group of neoplasms that can be located in the body soft tissues (muscles, fat, fibrous tissue). Our database has been kindly provided by the French Federation of Cancer Centers Sarcoma Group. Patients are usually followed up for 10 years to detect recurrences, but the physicians adapt the intensity and the methods of follow-up according to the different risk factors.[24,25]

Patients treated for soft tissue sarcoma and in follow-up phase are at risk of 3 different types of events: local relapse, distant metastasis, and death before relapse. As the objective is to detect the first event early enough, these events can be considered as competing.

Data description. We used data of 1614 patients whose disease was diagnosed after 2005 and who were less than 85 years old at diagnosis. The data correspond to the records collected between January 2005 and January 2012. The patients included were between 18 and 85 years old, with a median age of 58 years. and 50.2% of them were men. After a median follow-up of 28.5 months, 109 patients had died and the 2- and 5-year overall survival rates were estimated to 98.2% and 86.8%, respectively. According to the first event, 203 patients had loco-regional relapses, 174 had distant metastases, and

Table 2 Jeong and Fine Model Estimation Results ($\times 10^2$ if not specified otherwise)

	Local Relapse	Distant Metastasis	Death without Relapse
$\alpha_k(\times s)$	–9.31 (4.72)	–9.38 (5.08)	–2.08 (13.44)
$\beta_k(\times s)$	5.32 (0.58)	4.54 (0.54)	0.42 (0.14)
$F_k(5\ years \times s)$ (%)	21.69 (1.59)	18.81 (1.51)	2.32 (0.59)
$F_k(\infty)$ (%)	43.50	38.39	18.11

Note: Standard deviation (s) of α_k and β_k were obtained by maximum likelihood estimation. Standard deviation of $F_k(5\ years)$ was estimated using the multivariate delta method. The values of s of $F_k(\infty)$ are not presented, as they are not interpretable.

21 died before relapse. The nonparametric cumulative incidences have been estimated using the approach proposed by Kalbfleisch and Prentice.[19] This approach is implemented in the R package *cmprsk*.[26] The 5-year cumulative incidences of loco-regional relapse, distant metastasis, and death before relapse were, respectively, 20.5% (95% CI 17.5%–23.5%), 18.2% (95% CI 15.2%–21.3%), and 3.5% (95% CI 1.8%–5.2%). The goodness of fit of the data to a Jeong and Fine model has been assessed graphically.

Estimation without covariates. The first stage of the loss function calculation process is the estimation of the Jeong and Fine model parameters. These estimates are given in Table 2. The estimated cumulative incidences at 5 years are close to those estimated with nonparametric methods as shown in the table. The probability of experiencing an event during the first 5 years is 42.8%, with approximately a quarter of them (21.7%) corresponding to local recurrences as first event; 18.8% of the patients will experience distance metastasis as first event and 2.3% will die without having relapsed. If the follow-up is conducted for the entire lifetime, 43.5% and 38.39% of patients will have local relapse and distant metastasis, respectively. The others will die without relapsing. The parametric estimates of CIF for the 3 event types are shown in Figure 3A. Nonparametric estimations have also been plotted for comparison: Parametric and nonparametric curves are very similar.

Considering that the probability to be cured for a local relapse detected early is $\nu_1 = 0.80$, that the one for distant metastasis is $\nu_2 = 0.05$, and that there is obviously no cure to death $\nu_3 = 0$, the corresponding loss functions have been computed and plotted in Figure 3B. The loss function associated with death is null, and the one associated with distant metastasis is very low. As the prognosis of this type of relapse is poor, it is not useful to extend follow-up in order to diagnose this event. The overall loss function is very close to the loss function associated with local recurrence. Figure 3C shows this function with variability measures. It is shown that, for example, if the surveillance is stopped after 7 years, 14.1% (95% CI 5.1%–33.3%) of the patients will be lost. In this case, it is rather difficult to take a decision about the length of the surveillance. This could be easier after segmenting the population according to covariates.

Estimation with a covariate. Histological grade is considered as the most important prognostic factor for soft tissue sarcomas.[27] It is a 3-grade summary measure of the prognostic information (tumor differentiation, mitotic index, and importance of tumor necrosis). In our example, 1407 observations of the histological grade were available. The description of the recurrences according to this factor is presented in Table 3.

The estimation of the parameters of the model is given in Table 4. Six log hazard ratios are estimated, 2 for each event type. The reference category of this variable chosen for the modeling is grade III. γ_{1k} (respectively γ_{2k}) corresponds to the log of the hazard ratio of the grade I (respectively grade II) relative to grade III for a relapse of type k. These parameters provide materials to estimate the corresponding parametric cumulative incidence functions (Figure 4).

The loss functions present different patterns according to histological grade. The previous probabilities ν_k to be treated successfully in case of relapse of type k have been kept. The loss function estimated for patients with a grade I takes small values. Those estimated for patients with grades II and III have higher values. Even if there are more relapses for patients with a grade III than for patients with a grade II, the values of the loss function for patients with a grade III are not higher than those of the loss function for patients with a grade II. In fact, most of the relapses that are observed in grade III patients are distant metastasis. These have low cure rates and affect only slightly the loss function (Figure 4).

For example, if the threshold value, considered by the clinician, is 15%, the surveillance for individuals with grade I cancer could be stopped after 28 months. The individuals of grades II and III should be followed much longer (62 and 53 months, respectively). Otherwise, if the threshold value is 10%, the patients of grade I group could be in the

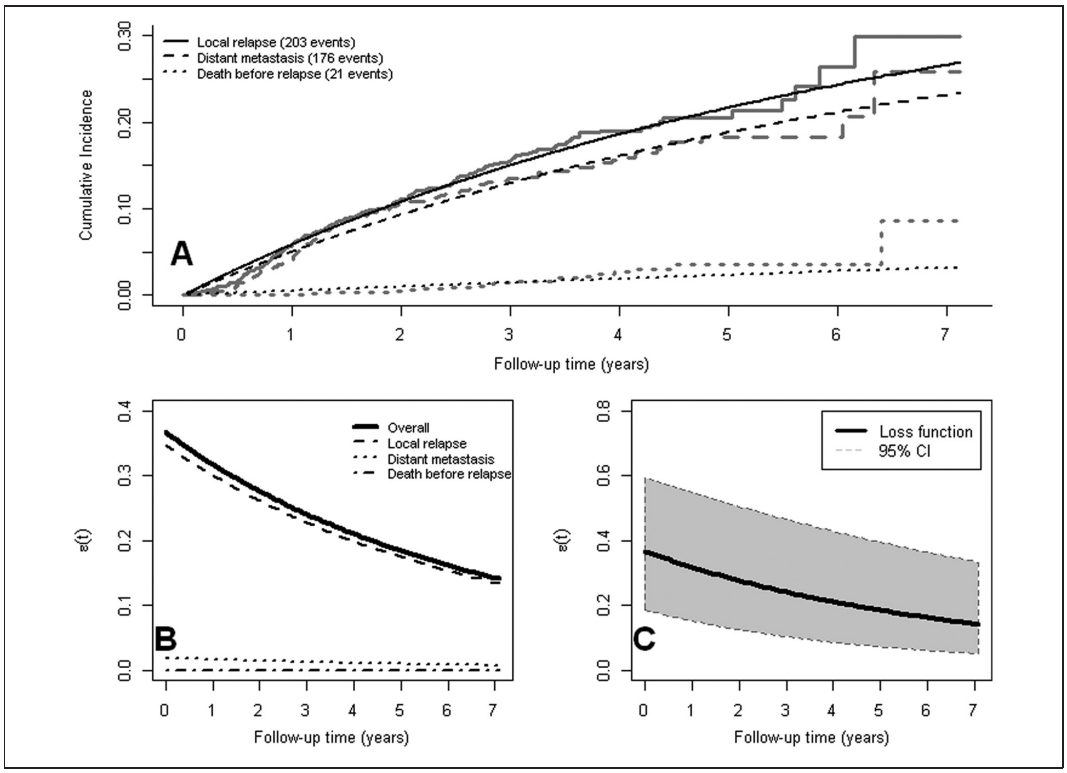

Figure 3 (A) Estimated cumulated incidence function by Jeong and Fine approach and by nonparametric approach. Black lines are parametric estimation by Jeong and Fine model, and gray lines are nonparametric estimations. (B) Loss function associated to each type of relapse and overall. (C) Overall loss function with 95% confidence interval.

Table 3 Description of the Population According to the Histological Grade (5-Year Cumulative Incidence Computed with the Nonparametric Approach)

		5-Year Cumulative Incidence % (Standard Deviation $\times$ 10^2)		
Histological Grade	***n* (%)**	**Local Relapse**	**Distant Metastasis**	**Death without Relapse**
I	399 (28.36)	15.77 (3.00)	5.36 (1.86)	2.99 (1.42)
II	470 (33.40)	27.47 (3.43)	16.66 (1.14)	3.76 (1.81)
III	538 (38.24)	19.00 (2.34)	31.84 (3.26)	4.41 (1.81)
Total	1,407 (100,00)	20.52 (1.53)	18.24 (1.56)	3.46 (2.72)

surveillance phase for 60 months but the duration will be 85 months for the others. We can note here the importance of the weighting parameters. More relapses occur in the grade III group than in the grade II group. But most of these relapses are metastases that have poor prognoses. Patients may not be followed for metastasis.[28] In this case, patients are followed principally for LR.

Table 4 Parameters Estimated by Jeong and Fine Proportional Hazard Model According to Histological Grade

Event Type	Local Relapse	Distant Metastasis	Death without Relapse
$\alpha_k(\times 10^3)$	−11.73	−14.28	−3.61
$\beta_k(\times 10^3)$	5.41	9.70	0.53
γ_{1k}	−0.38	−2.23	−0.31
γ_{2k}	0.26	−0.83	−0.29
$F_k(5\ years/GradeI)$ (%)	14.75	4.13	3.13
$F_k(5\ years/GradeII)$ (%)	25.98	15.68	2.13
$F_k(5\ years/GradeIII)$ (%)	20.78	32.35	2.84
$F_k(10\ years/GradeI)$ (%)	21.22	5.84	8.49
$F_k(10\ years/GradeII)$ (%)	36.21	21.57	3.81
$F_k(10\ years/GradeIII)$ (%)	29.41	42.69	5.07

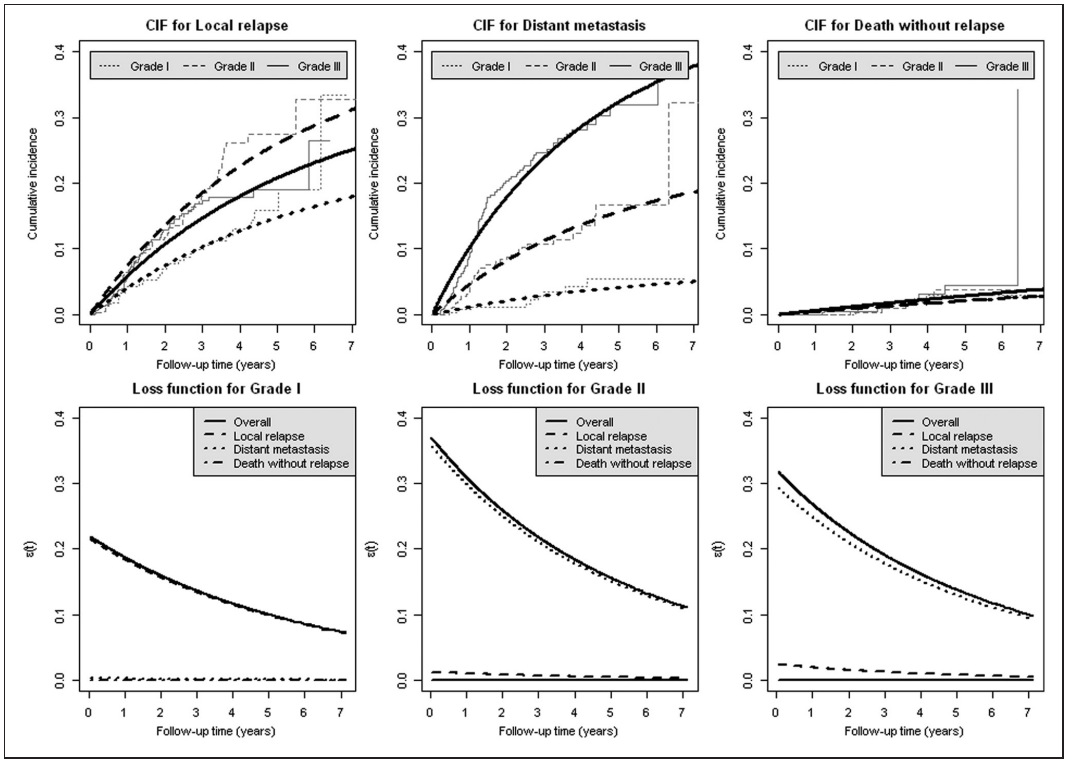

Figure 4 *(Above) Cumulative incidence functions according to the grade, by type of relapse. Black lines are parametric estimations by Jeong and Fine model, and gray lines are nonparametric estimations. (Below) Loss functions associated to each type of relapse and overall by grade.*

DISCUSSION

The proposed method is an extension of the method proposed by Mould and others[14] to determine the length of posttherapeutic follow-up according to the probability of observing an event of interest. Our extension takes into account several competing events. The method developed permits the individualization of the length of follow-up according to prognostic factors. The loss function is an effective decision-making tool for determining the length of the surveillance phase for patients treated for cancer. It adapts to different types of relapse as well as to individual patient characteristics. Finally, it is based on a flexible modeling approach that is easy to interpret.

The model by Mould and others estimates the probability for a patient who could have been successfully treated if diagnosed to relapse after the end of his or her surveillance. In fact, patients in posttherapeutic phase are at risk of several types of recurrences, which have different associated risk functions and are not influenced by prognostic factors in the same manner.

The modified Gompertz model is only applicable when the hazard functions decrease with time. Before this method is used, the goodness of fit of the data to the Jeong and Fine model should be tested. The Gompertz CIF for recurrence of type k increases with time and has a horizontal asymptote in p_k. In this sense, its derivative function, which is a modified form of the hazard function, is always decreasing. This model could not be applied to a distribution where the hazard is not decreasing with time. If the hazard is constant or increases, the CIF will never converge to a horizontal asymptote and the patients should be followed lifelong. So we could not estimate the length of posttherapeutic follow-up when hazard functions are nondecreasing. In case of nondecreasing hazard functions, parametric mixture models have been proposed to model the time before outcome in the presence of competing risks.[29]

In the application of the model, metastatic relapses are very common in patients treated for breast cancer as well as in patients treated for soft tissue sarcomas. However, these have a small impact on the loss function. As a matter of fact, at the current level of knowledge, practitioners commonly accept that the probability of being successfully treated for metastatic relapse is low.

The loss function can also be adapted to take into account prognostic factors. Once again, the application has shown the effect of histological grade on metastatic recurrence after treatment for soft tissue sarcoma. However, this factor does not significantly influence local and regional recurrence or death before recurrence. Continuous predictor variables may be used for defining the duration of posttherapeutic follow-up. From a statistical point of view, the use of continuous variables may improve the prognosis classification and yield a more accurate prediction. But in order to promote our method in clinical practice, the conservative approach to use categorical variables will be easier.

The direct approach for cumulative incidence modeling assumes a parametric form of the CIF. This model is more suitable than the Fine and Gray model for small sample sizes and for long-term prediction. As the CIF of each cause is modeled separately with distinct parameters, it is also more flexible than the classic model of Fine and Gray.[19,30] In this sense, it has been recommended in cases in which the purpose is to estimate the CIF and not the hazard function.[20,21] The Jeong and Fine model is very parsimonious compared with the methods usually found in the literature for CIF estimation.[31,32] Moreover, the results produced by the direct approach are similar to those produced with the classic approach of competing risks.[20,21]

The regression models have been restricted to a proportional hazards model. Jeong and Fine have proposed a more general form of the model.[21] This global form provides more flexibility for the estimators but is not easy to interpret and causes some difficulties of resolution because of the number of parameters. Hudgens and others[31] discussed the principal limitation of the method. The parametric distributions associated with the CIF are designed independently of each other. In this case, even if the probability of each event is less than 1, it is not guaranteed that the sum of the probabilities will be 1 when there is no cure fraction and $(1 - \pi)$ when there is a cure fraction π.

The probability that a patient will relapse before the end of the follow-up and the probability that he or she will be successfully treated can be estimated with the material used for the computation of the loss function. The parameter ν_k can also be interpreted in terms of cost.

The loss function helps the clinician to determine the duration of the surveillance. It provides output that depends on the specific threshold value, which must be chosen carefully. In fact, if this value is too high, a larger proportion of patients will miss the opportunity to benefit from a treatment while their

relapse is still in a preclinical phase. These relapses will then be detected at a clinical phase when care will be more costly and the prognosis poorer. However, if the specific threshold value is too small, the surveillance will take a long time and may generate various harms for the patient and supplementary costs for the health care system. Therefore, the model cannot take into account the harms and costs associated with a long follow-up. The only parameter taken into account is the proportion of patients who could not be detected early and treated with a curative intent. This is a limitation of the present approach. In fact, for cases where the hazard function of one type of recurrence is not decreasing, the Gompertz assumption will not be applicable. The determination of the length of the follow-up should be made according to these harms and costs.

Moreover, the loss function can be improved to be more accurate. The loss function should take into account an estimation of the probabilities of treatment success ν_k. These have been taken as fixed parameters. But they strongly depend on the individual characteristics of the patient and the relapse-free interval (time between the end of the treatment and the date of recurrence). This specification needs to be added to the model. Another aspect in determining the length of surveillance is the modality of detection of recurrence. The model should handle the recurrences detected during a planned follow-up visit differently than the recurrences detected at an unscheduled visit for symptomatic patients. Because recurrences detected via symptoms always reach late stages, they have unfavorable prognosis. The surveillance schedule should aim to detect recurrences at very early stages, where they are still asymptomatic, in order to start the treatment while the patient has a good prognosis.

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Chapitre III

Programmation optimale de la surveillance post-thérapeutique

I Problématique

Une fois que la durée de la surveillance d'un patient est définie après son traitement, il est important de s'intéresser au rythme de suivi. En effet, les patients ne sont pas soumis au mêmes rythmes de suivi. De plus, bon nombre de récidives sont encore découvertes en phase clinique symptomatique entre deux visites. Francken *et al.* [41, 42] ont observé cet état de fait dans trois quart des cas chez les patients traités de mélanomes. La solution pour détecter les récidives de façon précoce serait donc de programmer des visites très fréquentes. Ceci entrainerait une charge importante pour les patients et engagerait nécessairement des coûts élevés.

La détection précoce des récidives ne trouve son utilité que si le traitement administré présente un pronostic sensiblement meilleur entre la phase précoce et la phase tardive. Smith et Bear [40] résument la question en se demandant : *« Vaut-il vraiment mieux*

savoir très tôt que l'on a une métastase incurable que de croire que l'on se porte bien quand on se sent bien ? ». Alors que le postulat dans l'organisation des suivis post-thérapeutiques est encore de programmer les visites dans les périodes où le risque de récidive est le plus élevé [46], ne devrait-on pas aller au-delà et prendre en compte les options thérapeutiques disponibles ?

Différentes stratégies sont proposées dans la littérature pour la planification des calendriers de surveillance. Tsodikov *et al.* [47] ont proposé de modéliser le temps mis par une cellule cancéreuse pour devenir une tumeur détectable. Ils ont ensuite étudié la distribution du temps minimum d'apparition d'une telle tumeur. Le calendrier optimal proposé correspond ensuite à celui, en n visites, qui minimisera le temps entre l'apparition d'une éventuelle tumeur et sa détection. Une approche très différente est proposée par Inoue et Parmigiani [48]. Ceux-ci proposent l'estimation bayésienne des risques de récidive un utilisant une nouvelle famille de distribution Gamma. Le calendrier optimal de visites proposé est alors un choix séquentiel de temps de visites selon une approche dynamique. Filleron *et al.* [37] proposent enfin une troisième approche pour la détermination des délais entre deux visites successives. Leur approche, en deux étapes, permet de déterminer un calendrier de visites régulières. La distribution du risque de récidive est d'abord estimée selon un modèle paramétrique, par rapport aux données. La fonction cumulative correspondante est ensuite définie. Les dates r de visites sont alors programmées aux quantiles d'ordre r de sorte à ce que les risques de récidives soient identiquement distribuées dans chaque intervalle. Les méthodes proposées ne permettent cependant pas de prendre en compte les effets induits par un diagnostic tardif. Elles se limitent en effet à l'estimation du délai avant l'apparition de la récidive, sans prendre en compte les effets de son évolution en phase clinique.

Le principe de la détection précoce des récidives est basé sur l'histoire naturelle de la maladie. Cette histoire naturelle est modélisée par le passage de l'individu à travers plusieurs stades (indétectable, puis pré-clinique et clinique). Les outils de modélisation multi-états ont par conséquent été largement utilisés dans la littérature [39, 78, 79]. Des hypothèses sont à chaque fois émises pour des raisons de simplification sans pour autant s'éloigner de la complexité du phénomène observé. Les modèles multi-états par chaînes de Markov présentent l'avantage de permettre cette description des processus passant

par plusieurs états différents. Une approche nouvelle, fondé sur l'histoire naturelle de la maladie, est proposée pour la détermination d'un calendrier optimal de surveillance post-thérapeutique.

II Objectifs

L'objectif de ce chapitre est de proposer une stratégie permettant de définir des dates optimales pour la programmation des visites dans le cadre de la surveillance post-thérapeutique du cancer. Le calendrier est déterminé de sorte à maximiser la probabilité de détecter une récidive en phase précoce et à minimiser celle de passage en phase clinique entre deux visites consécutives.

III Méthodes

III.1 L'approche de Zelen

La méthode est inspirée des travaux de Marvin Zelen [26]. Celui-ci s'est basé sur l'histoire naturelle de la maladie dans le cadre du dépistage du cancer. L'histoire naturelle est caractérisée par un modèle en trois états successifs (figure III.1) : l'état Sain, la phase Pré-clinique et la phase Clinique.

Figure III.1 – Modèle d'histoire naturelle de Zelen

Soit $[0, T]$ l'intervalle dans lequel sont programmées $n + 1$ visites de dépistage à des dates $t_i, 0 \leq i \leq n$ ordonnées dans le temps. Soit β la sensibilité de l'examen effectué pendant les séances de dépistage, c'est-à-dire la probabilité que l'examen ne détecte pas une tumeur alors que celle-ci est déjà présente.

Zelen définit $I_r(\beta, t)\mathrm{d}t$ comme la probabilité, pour un individu participant à un programme de dépistage avec une sensibilité β, de transiter de la phase pré-clinique à la phase clinique de la maladie dans l'intervalle $(t, t+\mathrm{d}t)$, avec $t_{r-1} \leq t < t_r, (r = 1, 2, \ldots n)$.

Par suite, $I_r(\beta)$ est la probabilité de transiter en phase clinique entre les visites t_{r-1} et t_r. Zelen définit ensuite $D_r(\beta)$ comme étant la probabilité qu'un cancer soit détecté en phase pré-clinique chez un patient lors de la séance de dépistage organisée à la date t_r, sachant la sensibilité β. Par suite, il propose la fonction d'utilité suivante, en choisissant judicieusement les coefficient A_0, A et B :

$$U_{n+1} = U_{n+1}(\beta, T) = A_0 D_0(\beta) + A \sum_{r=1}^{n} D_r(\beta) - B \sum_{r=1}^{n} I_r(\beta). \tag{III.1}$$

La maximisation de cette fonction d'utilité permet de déterminer les n dates t_r optimales pour la planification de la surveillance.

III.2 Application à la surveillance

La méthode proposée par Zelen [26] peut être adaptée pour organiser la surveillance post-thérapeutique. Le modèle d'histoire naturelle considéré pour la surveillance est défini en $2K+1$ états où K représente le nombre de types différents de récidives considérés (figure III.2). Le patient en phase post-thérapeutique ne présente plus de tumeur (état *Sain*) à l'issue du traitement. En cas de récidive d'un type $k, (k = 1, 2, \ldots K)$ donné, celui-ci passera en phase pré-clinique (état $Prec_k$). Si cet événement n'est pas détecté assez tôt, il migrera dans la phase clinique du type de récidive (état $Clin_k$).

La durée de surveillance $[0, T]$ est divisée en une partition de n intervalles où n est le nombre de visites. La distribution du temps avant l'apparition de la phase précoce de chaque type de récidive ainsi que l'intervalle entre l'apparition de la phase précoce et le passage en phase tardive sont ensuite modélisés.

Les modèles sont tous fondés sur une hypothèse de chaînes de Markov homogènes. Il est alors possible de déterminer la probabilité qu'un patient soit dans un état donné à une date de visite donnée. Cette probabilité prend en compte la sensibilité des examens effectués lors des visites précédentes. Nous définissons ainsi :

$I_{rk}(\beta)$ la probabilité qu'un individu, en phase de surveillance, transite de la phase pré-clinique à la phase clinique d'une récidive de type k entre les visites t_{r-1} et t_r ;

$D_{rk}(\beta)$ la probabilité qu'un individu, en phase de surveillance, soit détecté en phase pré-clinique d'une récidive de type k au cours de la visite t_r.

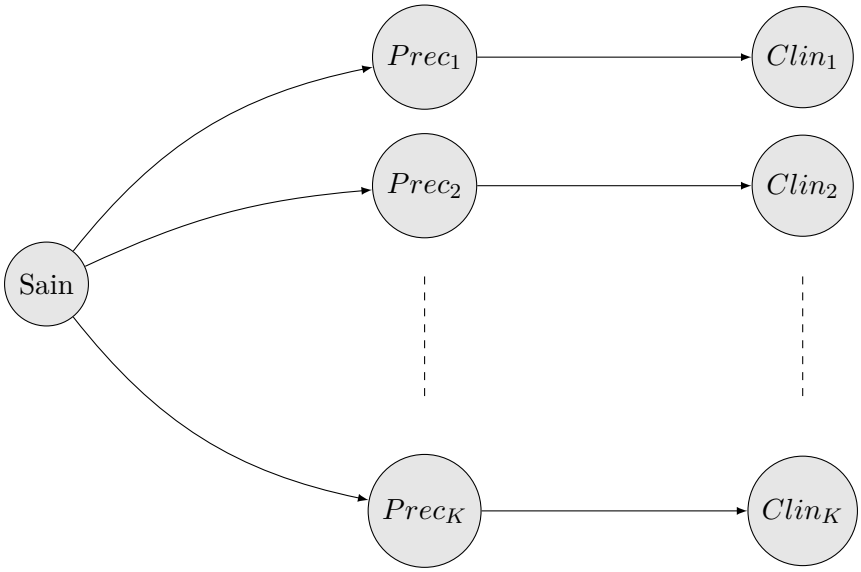

FIGURE III.2 – Modèle d'histoire naturelle pour la surveillance

Une fonction d'utilité peut alors être construite à la manière de Zelen. Cette fonction est une combinaison linéaire des probabilités définies. Les pronostics de guérison correspondant aux types de récidives que ce soit en phase pré-clinique ou clinique sont utilisés comme coefficients de pondération. En ce sens, la fonction d'utilité est adaptée aux traitements et aux équipements utilisés pour la surveillance. La fonction retourne une utilité relative à chaque calendrier composé de $n-1$ dates de visites comprises entre 0 et T. Le calendrier optimal sera celui qui maximise la fonction d'utilité.

La méthode proposée permet aussi d'estimer le nombre de visites (le nombre de patients toujours en surveillance) après un nombre de visites donné ainsi que le nombre total de visites à effectuer pour une cohorte de patients. Il est par suite possible de l'utiliser pour des planifications dans un centre de prise en charge ou pour une analyse économique.

IV Article : Programmation optimale de la surveillance.

L'ensemble des méthodes décrites a été publié dans la revue ***Statistical Methods in Medical Research***. Elles ont ensuite été appliquées pour définir un calendrier de

surveillance optimal pour des patients traités d'un cancer de la tête ou du cou. Les paramètres pour la définition de l'histoire naturelle de la maladie ont été inspirés de Ritoe *et al.* [39]. Les différents calendriers obtenus par modélisation ont été ensuite comparés à ceux les plus souvent utilisés aux États-Unis, en Europe et plus particulièrement en France. À chaque fois, le calendrier optimal permettait d'aboutir à une meilleure utilité et à un moindre nombre de visites.

Article

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Optimal scheduling of post-therapeutic follow-up of patients treated for cancer for early detection of relapses

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Abstract

Post-therapeutic surveillance is one important component of cancer care. However, there still is no evidence-based strategies to schedule patients' follow-up examinations. Our approach is based on the modeling of the probability of the onset of relapse at an early asymptotic or preclinical stage and its transition to a clinical stage. For that we consider a multistate homogeneous Markov model, which includes the natural history of relapse. The model also handles separately the different types of possible relapses. The optimal schedule is provided by the calendar visit that maximizes a utility function. The methodology has been applied to laryngeal cancer. The different follow-up strategies revealed to be more efficient than those proposed by different scientific societies.

Keywords

post-therapeutic follow-up, optimal scheduling, cancer, natural history, multistate Markov model, utility function

1 Introduction

There has been a great interest in the literature related to cancer screening.[1–6] Computational methods have been proposed to help clinicians to decide whether or not to screen patients for early detection of cancer.[7] The use of mathematical modeling to organize screening programs has been extensively developed.[3,4] Multistate modeling has been used to describe the natural history of

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cancer[8,9] and to evaluate different screening programs.[10–12] This has then been extended to propose optimal screening calendars for early detection of cancer.[13–19] A large part of this methodology makes the assumption that the earlier cancer is detected the better are the chances of cure. For example, the maximization of a utility function proposed by Zelen[13] provides a calendar for screening which maximizes the probability of detection of a disease at a preclinical stage and minimizes the probability of detection at a late clinical stage.

In oncology, another important concern of cancer care is the post-therapeutic follow-up period with numerous objectives.[20] Patients are usually monitored at regular intervals to detect disease relapses in order to propose therapeutic interventions with curative or palliative intent. There is actually no evidence-based method to determine a follow-up schedule for patients treated for cancer. The surveillance calendars are generally based on experts recommendations. Different scientific societies have proposed their recommendations for the post-therapeutic follow-up schedule of cancer, according to their site, such as oral cancers.[21–23] These schedules are generally easy to apply but are not necessarily adapted for detecting cancer-related events in an optimal manner.[24,25] As the incidence of cancer increases and the mortality decreases due to the implementation of screening programs and therapeutic progress,[26] the number of patients in the post-therapeutic phase is increasing. As a consequence, the follow-up workload grows every year, implying an increase in the associated financial needs. The importance of these costs is eventually due to a large number of unnecessary visits and false positive examinations.[27]

Many relapses however are still diagnosed after the onset of symptoms between two scheduled visits.[28,29] For this consideration, Wheeler et al.[30] estimated that the follow-up visits should be scheduled when the risk of relapse is high. Filleron et al.[25] have proposed a two-step algorithm, based on individual patient characteristics, to determine visit dates. Recently, Somda et al.[31] have proposed a loss function which permits to determine the optimal length of post-therapeutic follow-up using competing risks methodology.

The existing methods do not take into account the different steps of the natural history of the disease. As for cancer screening programs, post-therapeutic surveillance is only useful when recurrences are detected at early stages as the prognosis is better.[32,33] An optimal follow-up schedule should maximize the probability of detecting patients in a preclinical phase and treating them successfully. A patient is said to be in a preclinical stage when he/she has no symptom of relapse. In this case, his relapse can only be detected by a specific examination. The treatments are shown to be much more efficient for some relapse types when they are undertaken at this stage of the disease. The optimal schedule should also minimize the futile visits. Another specific aspect of post-therapeutic follow-up is that patients are at risk of different types of events. These have different characteristics and should be modeled differently. The importance of surveillance also differs regarding the type of relapse as it may be less important to optimize follow-up for an early detection of metastasis especially in the absence of curative treatment options.[34]

The objective of this paper is to propose a decision-making tool to determine an optimal scheduling of follow-up visits for patients treated for cancer. We propose a calendar with a given number of visits over a fixed time period that will permit to detect the eventual relapses as soon as possible after their occurrence, as they still are in an early preclinical stage. This method also distinguishes the different relapse types in order to be more sensitive to the event types with better prognosis. The proposed method is an adaptation of the utility function developed by Zelen[13] for screening programs. The utility function will be formulated for post-therapeutic follow-up by taking into account the natural histories of the different relapse types. Section 2 provides background, presenting the approach of Zelen for optimal cancer screening programs. Section 3 formulates the general problem for post-therapeutic follow-up and presents the

utility function. An application on laryngeal cancer patients follow-up is presented in Section 4. Finally, Section 5 provides a conclusive discussion.

2 Background

The use of scheduled examinations to detect chronic disease is widely studied in the literature. In the case of cancer screening, Zelen has proposed an approach to determine optimal scheduling for diagnosis. The main objective of this approach is to maximize the proportion of patients detected asymptomatically at screening visits and to minimize the proportion of clinically diagnosed patients between two consecutive schedule visits. This last quantity corresponds to interval cancer. Three states of the disease are considered according to the natural history (Figure 1). At the initial stage, the patient is free of disease. This is the healthy state, which will be noted by S_0. The state S_0 also includes the event of having the disease with no sign or symptoms, but which cannot be diagnosed by any available diagnostic procedure. S_p corresponds to a preclinical stage, where the patient unknowingly has the disease which can only be detected through specific examinations (asymptomatic stage). Without appropriate treatment, a patient will move from preclinical to clinical stage, denoted by S_c. At this stage, the disease presents obvious symptoms and is clinically diagnosed through simple examination. So examinations are performed for individuals in S_0 stage in order to detect the transition to S_p early enough before they move to S_c. These examinations are not 100% efficient. The sensitivity β is defined as the probability of detecting a patient who is in the preclinical stage (S_p) during a scheduled examination.

Let $P(t)$ be the probability of being in S_p at time t. $\omega(t)$ and $I(t)$ are defined as the transition intensity from $S_0 \rightarrow S_p$ and from $S_p \rightarrow S_c$, respectively. Finally, $q(t)$ is defined as the probability density function of the sojourn time in S_p, and $Q(t) = \int_t^\infty q(x)dx$.

$[0; T]$ is the interval time in which $(n+1)$ examinations are to be performed at ordered time points $0 = t_0 < t_1 < t_2 < \cdots < t_n = T$. Zelen has proposed a formula to calculate two probabilities to evaluate the performance of a screening program. The probability of detection $D_r(\beta)$ is the probability that the disease is detected in preclinical stage at the rth screening examination (scheduled at the date t_r), when the sensitivity is β. The incidence $I_r(\beta)$ is the probability that an individual, participating in an early detection program with sensitivity β, and whose disease has not been detected in the preclinical stage, is diagnosed in clinical stage within the interval $[t_{r-1}, t_r)$. Finally, an individual participating in a screening program with sensitivity β will either be detected in preclinical stage at a given visit r with probability $D_r(\beta)$ or transit to a later stage between visits $r-1$ and r with probability $I_r(\beta)$.

Figure 1. Representation of the screening model by Zelen.

The objective of screening is to maximize the first probability, $D_r(\beta)$, and to minimize the second one, $I_r(\beta)$. Zelen proposed a utility function which is a linear combination of both probabilities. For given coefficients A_0, A, and B, the utility function U_{n+1} is given by

$$U_{n+1} = U_{n+1}(\beta, T) = A_0 D_0(\beta) + A \sum_{r=1}^{n} D_r(\beta) - B \sum_{r=1}^{n} I_r(\beta)$$

This function can be interpreted in many different manners, according to the nature of the coefficients. If these coefficients represent the probability of cure corresponding to the stage in which the diagnosis is made, then U_{n+1} will correspond to the difference in cure rates between patients diagnosed in scheduled visits and patients who have transited to late stage. If the coefficients are equal weights, $(A/B = 1)$, then U_{n+1} is proportional to the difference in the expected value of cases detected on examination compared to the cases occurring between screening visits. The time points which maximize this utility function will be the optimal examination dates for the patients screening strategy.

The utility function proposed by Zelen was developed for the purpose of screening for cancer. It is less adequate in post-therapeutic follow-up. In fact, patients entering in post-therapeutic follow-up are at risk of several different recurrence types as a first event: local recurrence, second cancer, distant metastasis, etc. The relevance of early detection is clearly dependent on the first event type. If no treatment exists for curing an event type, then detecting early this event type will have little or no impact on overall survival. In the majority of cancer types, this is the case for the detection of distant metastases even for patients in an asymptomatic stage.[34,35]

We propose in the following sections an adaptation of the approach proposed by Zelen which is more suitable to post-therapeutic surveillance.

3 Methods

3.1 Notations

During post-therapeutic follow-up patients are at risk of K types of events (local or regional relapse, second cancer or metastatic relapse for example). For each event type k, $(k = 1, 2, \ldots, K)$, the preclinical state of the recurrence is denoted by S_{pk} (asymptomatic stage) and the corresponding clinical state by S_{ck} (symptomatic stage) (see Figure 2). We denote S_0 the healthy state. Under this multistate model, $\omega_k(t)$ is the transition intensity from S_0 to S_{pk}, where t is the time since patients enter into the post-therapeutic follow-up phase, i.e., after the end of treatment. $f_k(t)$ is the associated probability density function. The transition intensity to any preclinical state is then given by $\omega(t) = \sum_{k=1}^{K} \omega_k(t)$.

We define $\lambda_k(z)$ as the transition intensity from S_{pk} to S_{ck}, where z is the time since the patient enters the preclinical state of a relapse of type k. The associated probability density function is $q_k(z)$ and the specific survival function is denoted by $Q_k(z)$.

Patients are followed for a total duration of T months with n scheduled visits at fixed time periods t_r; $r = 1, 2, \ldots, n$ with $0 < t_1 < \cdots < t_n = T$. The rth interval is defined as the interval $[t_{r-1}, t_r)$. When a patient moves from state S_{pk} to S_{ck} within a given rth interval, he is said to be an incident case of that interval (interval relapse). At each scheduled follow-up visit, specific examinations are performed to detect relapses in a preclinical phase (asymptomatically).

Let β_k be the sensitivity of an exam to detect an event of type k in preclinical stage. Let us define $D_{rk}(\beta_k)$ as the probability of detecting an event of type k in a preclinical state at the

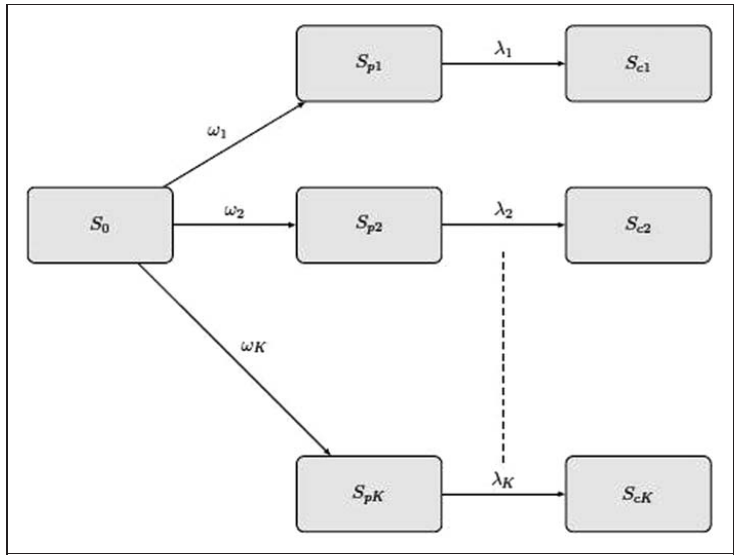

Figure 2. Representation of the post-therapeutic follow-up model.

rth visit and $I_{rk}(\beta_k)$ the probability of occurrence of a clinical state of an event of type k in the rth interval.

3.2 Hypotheses and assumptions

Figure 2 presents the $2K + 1$ states of the model and the associated transition probabilities. Further assumptions are made for these transition probabilities: (i) The different event types are considered mutually exclusive or competing, so a patient can experience only one event type. In fact, as soon as a relapse is detected, regardless of the type, the patient returns to a treatment phase and thus leaves the surveillance phase, so the occurrence of another event type can be ignored in the model specification. (ii) A patient in a preclinical state of a given event type is only at risk of transiting to a clinical state of the same event type. In fact, as the objective of the follow-up is to detect early enough any relapse before it transits to a clinical stage, the effect of the occurrence of a second relapse type is not taken into account in the utility function.

The model is based on a multistate regular homogeneous Markov assumption.[12] The properties of such a model are the following:

- The transition rates are invariant with time $\left\{ \omega_k(t) = \omega_k, \quad \lambda_k(z) = \lambda_k \right\}$.
- The distributions of the sojourn times in the different states are defined as $\left\{ f_k(t) = \omega_k e^{-\omega t}, \quad q_k(z) = \lambda_k e^{-\lambda_k z} \right\}$ with $\omega = \sum_{k=1}^{K} \omega_k$. The sojourn times in successive states are independent.
- The probabilities of transition from one state to another are independent of the past visited states and independent of the time spent in these states.

3.3 Probabilities of detecting an event at the first visit

A patient can experience the two states of relapse before the first visit. In this case, he will first move from the S_0 state to a S_{pk} state and then to the corresponding S_{ck} state before t_1.

Let I_{1k} be the probability of having an incident case of relapse of type k in the first interval, e.g., the probability of entering a clinical phase for relapse type k before t_1. We have

$$I_{1k} = \int_0^{t_1} f_k(x)\{1 - Q_k(t_1 - x)\}dx = \frac{\omega_k}{\omega}\left(1 - e^{-\omega t_1}\right) - \frac{\omega_k}{\lambda_k - \omega}\left(e^{-\omega\, t_1} - e^{-\lambda_k t_1}\right)$$

Let $D_{1k}(\beta_k)$ denote the probability that a relapse of type k is detected at the first visit, when the sensitivity to detect relapse type k is β_k, The probability of this event is given by

$$D_{1k}(\beta_k) = \beta_k \int_0^{t_1} f_k(x)Q_k(t_1 - x)dx = \beta_k \frac{\omega_k}{\lambda_k - \omega}\left(e^{-\omega t_1} - e^{-\lambda_k t_1}\right)$$

3.4 Probabilities of detecting a relapse at the *r*th visit

As for the first interval, a patient could successively experience a transition from S_0 to S_{pk} and then from S_{pk} to S_{ck} in the rth interval. The probability of this event is the following

$$I^0_{rk} = \int_{t_{r-1}}^{t_r} f_k(x)\{\ 1 - Q_k(t_r - x)\}dx$$

$$I^0_{rk} = -\frac{\omega_k}{\omega}\left(e^{-\omega\, t_r} - e^{-\omega\, t_{r-1}}\right) - e^{-\lambda_k t_r}\frac{\omega_k}{\lambda_k - \omega}\left\{e^{(\lambda_k - \omega)t_r} - e^{(\lambda_k - \omega)t_{r-1}}\right\}$$

A patient could also transit from S_0 to S_{pk} in a given ith interval, $i < r$ and then transit from S_{pk} to S_{ck} in the rth interval. That means that $r - i$ visits will fail to detect this event before the clinical phase. The probability of this event will then be

$$I^1_{rk}(\beta_k) = \sum_{i=1}^{r-1}(1 - \beta_k)^{r-i}\int_{t_{i-1}}^{t_i} f_k(x)\{\ Q_k(t_{r-1} - x) - Q_k(t_r - x)\}dx$$

$$I^1_{rk}(\beta_k) = \frac{-\omega_k}{\lambda_k - \omega}\left(e^{-\lambda_k t_r} - e^{-\lambda_k t_{r-1}}\right)\sum_{i=1}^{r-1}(1 - \beta_k)^{r-i}\left\{e^{(\lambda_k - \omega)t_i} - e^{(\lambda_k - \omega)t_{i-1}}\right\}$$

Finally, the probability of having an incident case of relapse of type k in the rth interval is given by

$$I_{rk} = I^0_{rk} + I^1_{rk}$$

The probability of detection of a relapse of type k during a follow-up visit is calculated in the same manner. The first event concerns a patient who is transient from state S_0 to state S_{pk} in the rth interval and whose relapse is detected at the rth visit. The probability of this event is given by

$$D^0_{rk}(\beta_k) = \beta_k \int_{t_{r-1}}^{t_r} f_k(x)Q_k(t_r - x)dx$$

$$D^0_{rk}(\beta_k) = \beta_k e^{-\lambda_k t_r}\frac{\omega_k}{\lambda_k - \omega}\left\{e^{(\lambda_k - \omega)t_r} - e^{(\lambda_k - \omega)t_{r-1}}\right\}$$

The second possibility concerns a patient who will transit from S_0 to S_{pk} in a given ith interval, $i < r$, and then be detected at the rth visit in the state S_{pk} before moving to state S_{ck}. The probability of this event is given by

$$D^1_{rk}(\beta_k) = \beta_k \sum_{i=1}^{r} (1-\beta_k)^{r-i} \int_{t_{i-1}}^{t_i} f_k(x) Q_k(t_r - x) dx$$

$$D^1_{rk}(\beta_k) = \beta_k e^{-\lambda_k t_r} \frac{\omega_k}{\lambda_k - \omega} \sum_{i=1}^{r-1} (1-\beta_k)^{r-i} \left\{ e^{(\lambda_k - \omega) t_i} - e^{(\lambda_k - \omega) t_{i-1}} \right\}$$

Similarly, the probability that a relapse of type k is detected at the rth visit, when the sensitivity to detect relapse of type k is β_k, is given by $D_{rk} = D^0_{rk} + D^1_{rk}$.

3.5 The utility function

A utility function is a function which assigns a real number to each possible option, in such a way that the higher the number, the more preferred is the option. The optimal decision corresponds to the one which maximizes the utility function. In the current case, the utility function should help in maximizing the probability of event detection at an early stage. Maximizing such a function should also minimize the probability of transition at a later stage. We propose a utility function which is a linear combination of the D_{rk} and the I_{rk} probabilities with respective weighting coefficients A_k and B_k. Let us define A_k as the probability, for a given patient, to be successfully treated after a relapse of type k early detected and B_k, the probability to be successfully treated after a relapse of type k diagnosed in clinical stage. Then the term $A_k D_{rk}$ represents the proportion of patients cured of a relapse of type k after detection in a preclinical state. The term $B_k I_{rk}$ also represents the proportion of patients cured of a relapse of type k while they were diagnosed in a clinical state. Our utility function will permit the maximization of the first proportion and the minimization of the second one.

Let us define the following vectors $\beta = (\beta_k)$, $A = (A_k)$, $B = (B_k)$, $I_r = (I_{rk})$, and $D_r = (D_{rk})$. $()'$ represents the vector's transposition notation.

If a follow-up is scheduled in n visits with a total duration of T where the sensitivity of the examination to detect a type k recurrence is β_k, the utility function is defined by

$$U_n(t_1, \ldots, t_{n-1}, T) = \sum_{r=1}^{n} A' D_r - \sum_{r=1}^{n} B' I_r$$

The utility function can be maximized by the Nelder and Mead[36] method. The values of t_r which maximize the utility function are the optimal dates where the follow-up visits should be scheduled.

3.6 Total number of scheduled visits

As the probability of having an incidence case between two consecutive scheduled visits and the probability of detection of a relapse during a scheduled visit are known, the number of individuals still at risk of recurrence can be estimated for each visit rank, in the absence of

censoring (i.e., death). Then, the total number of scheduled follow-up visits for a given follow-up schedule can be estimated, assuming that there is no loss of follow-up. For N individuals entering in the surveillance phase, the number of patients still at risk of recurrence at the rth visit can be calculated. This number corresponds to the number of visits to undertake at this visit. It can be expressed as

$$Nbvis_r = N \times \prod_{i=1}^{r} \left\{ 1 - \sum_{k=1}^{K} \left(I_{ik} + D_{(i-1)k} \right) \right\} \text{ where } D_{0k} = 0 \; \forall k = 1, \ldots, K$$

Then the total number of scheduled visits that will be held for N patients entering in surveillance phase is

$$Nbvis = \sum_{r=1}^{n} Nbvis_r$$

4 Application on follow-up after treatment for laryngeal cancer

4.1 Recommended follow-up strategies

Many different follow-up strategies have been proposed by scientific societies for post-therapeutic surveillance. For laryngeal cancer, the most current strategy in Europe is the one proposed by the European Society of Medical Oncology (ESMO).[23,37,38] The French Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC) proposed its own variant of this strategy.[21] Finally, the most used strategy in the United States is the one of the National Comprehensive Cancer Network (NCCN).[22] For a 10-year follow-up, the different strategies are presented in Table 1. A scheduling recommendation of a given scientific society may vary, depending on some prognostic factors such as grade. In our example, we always used a scheduling scheme which corresponds to the range of possibilities in the recommendations.

Schwartz et al.[39] have highlighted the inconsistency of the post-radiotherapy surveillance of head and neck cancer. They could not prove a correlation between intensive follow-up and patients' survival. Finally, the efficacy of the different follow-up strategies for head and neck cancers is still a matter of discussions.

The methodology developed in the previous section has been applied to a population of patients treated for laryngeal cancer. They are considered at risk of three different recurrence types: loco-regional relapse, distant metastasis and second primary cancer. The hazard functions, given as monthly hazard rates, corresponding to each of the three recurrence types were found in the literature.[37,38] As weighting values, the proportion of patients who underwent curative treatment after a recurrence detected in preclinical or in clinical stage was considered, for the same data source, according to the recurrence type. Finally, the sensitivity has been fixed to 80% for each recurrence type according to expert recommendations. The model parameters are presented in Table 2.

The utility function was computed for the different follow-up calendars, and the results are presented in Table 3. The values of this utility function for the recommended follow-up programs are 0.22, 0.11, and 0.13, respectively, for the ESMO, FNCLCC, and NCCN recommendations. With the proposed follow-up visits schedule, the probabilities to be cured after a recurrence detected at an early stage were 0.40, 0.33, and 0.35, respectively, for ESMO, FNCLCC, and NCCN schedules.

Table 1. Post-therapeutic surveillance strategies for laryngeal cancer follow-up according to three scientific societies.

	Year of post-therapeutic surveillance					
Year	1	2	3	4	5	6–10
ESMO (31 visits)	1 visit monthly	1 visit every 2 months	1 visit every 3 months	1 visit every 6 months	1 visit every 6 months	1 visit every 12 months
FNCLCC (20 visits)	1 visit monthly for 6 months then every 3 months	1 visit every 6 months	1 visit every 6 months	1 visit every 6 months	1 visit every 12 months	1 visit every 12 months
NCCN (18 visits)	1 visit every 3 months	1 visit every 4 months	1 visit every 6 months	1 visit every 6 months	1 visit every 6 months	1 visit every 12 months

ESMO: European Society of Medical Oncology; FNCLCC: Fédération Nationale des Centres de Lutte Contre le Cancer; NCCN: National Comprehensive Cancer Network

Table 2. Parameters for the model.

		Local & regional relapse	Metastasis	Second primary cancer
Intensity $S_0 \rightarrow S_{pk}$ ($.10^{-3}$)	ω_k	3.250	1.667	9.500
Intensity $S_{pk} \rightarrow S_{ck}$	λ_k	0.350	0.317	0.149
Cure after S_{pk}	A_k	0.737	0.000	0.923
Cure after S_{ck}	B_k	0.803	0.000	0.440
Sensitivity	β_k	0.800	0.800	0.800

Table 3. Comparison of probabilities of cure and utilities between recommended schedules, optimal schedules and reduced schedules with equivalent utilities, according to the different follow-up strategies for a 10 years surveillance period.

		Number of visits per patient	Total number of visits for 1000 patients	Probability early detection and cure	Probability late detection and cure	Utility
ESMO	Recommendation	31	24,108	0.40	0.18	0.22
	Optimal	31	20,804	0.44	0.16	0.28
	Reduced	25	16,836	0.41	0.18	0.23
FNCLCC	Recommendation	20	15,113	0.33	0.23	0.11
	Optimal	20	13,649	0.37	0.20	0.17
	Reduced	17	11,675	0.34	0.22	0.12
NCCN	Recommendation	18	12,685	0.35	0.22	0.13
	Optimal	18	12,287	0.35	0.22	0.14
	Reduced	18	12,287	0.35	0.22	0.14

ESMO: European Society of Medical Oncology; FNCLCC: Fédération Nationale des Centres de Lutte Contre le Cancer; NCCN: National Comprehensive Cancer Network

4.2 Optimal follow-up strategies

The optimal follow-up visit dates are obtained after maximization of the utility function for each surveillance program. For each follow-up recommended strategy, we have computed an associated strategy for a 10-year surveillance with the same number of visits per patient which maximizes the utility. The optimal visit dates, expressed in terms of the number of months after the end of the treatment, are shown in Figure 3. The maximal utilities obtained for a 10-year follow-up with the different numbers of visits are 0.28, 0.17, and 0.14 for the ESMO, FNCLCC, and NCCN programs, respectively.

The probabilities to be cured after a recurrence detected at an early stage are 0.44, 0.37, and 0.35 for the same number of visits as, respectively, ESMO, FNCLCC, and NCCN guidelines. These represent increases of the gain of more than one-tenth for the ESMO and the FNCLCC guidelines, for example. Moreover with the optimal schedule, there will be fewer patients treated after a late detection.

The probability of treating a patient after an early detection of a recurrence increases with the number of scheduled visits per patient. In contrary, the probability of treating a patient after a late detection decreases. This relationship is obvious: in fact, as the frequency of visits increases, the patients' recurrences will be more likely to be early diagnosed. Finally, the utility function increases naturally with the number of visits. There will then be less and less patients transiting in late clinical stage. Figure 4 (the graph at the top) represents the evolution of these two probabilities and of the utility function based on the number of scheduled visits. The values corresponding to the three recommendations are also plotted on the figure. This representation shows that utilities equivalent to those of the recommended schedules can be reached with fewer visits, if the schedule is optimal. Figure 4 (graphs at the bottom) also provides the proportion of patients who will be early detected according to an optimal follow-up schedule, by number of scheduled visits for each recurrence type. The follow-up strategies proposed by the scientific societies always lead to less early detections than the optimal schedule.

The optimal numbers of visits have been determined to reduce the recommended schedules without diminishing the value of the utility function. These are the smaller integers leading to a greater utility than the one provided by the corresponding recommendation. These schemes are presented in Figure 3 as reduced schedules and the corresponding attributes are presented in Table 3. So, for an equivalent utility, the ESMO guideline can be rearranged in 25 scheduled visits and the FNCLCC guideline will be rearranged in 17 visits. The number of visits of NCCN guideline could not be reduced but the scheduling should be reorganized.

4.3 Total number of scheduled visits

Finally, the expected total numbers of visits are calculated for each follow-up scheme. If 1000 patients enter in surveillance phase and if they are followed according to the ESMO recommendation with 31 scheduled visits per patient, 24,108 visits with the current examinations will be made during the 10 years of follow-up. Therefore, the utility will be 0.22. The optimal scheduling with 31 visits per patient will require 20,804 visits, leading to a utility of 0.28. The reduced schedule plans 25 visits per patient with a total of 16,836 visits in 10 years, leading to a utility of 0.23. As shown in Table 3, the optimal follow-up, compared to the recommended ones, permits important reductions in the total number of visits according to the guidelines. Considering the reduced schemes, the total number of visits can be strongly reduced. The values of the utility function for these reduced follow-up schedules are, respectively, 0.23, 0.12, and 0.14.

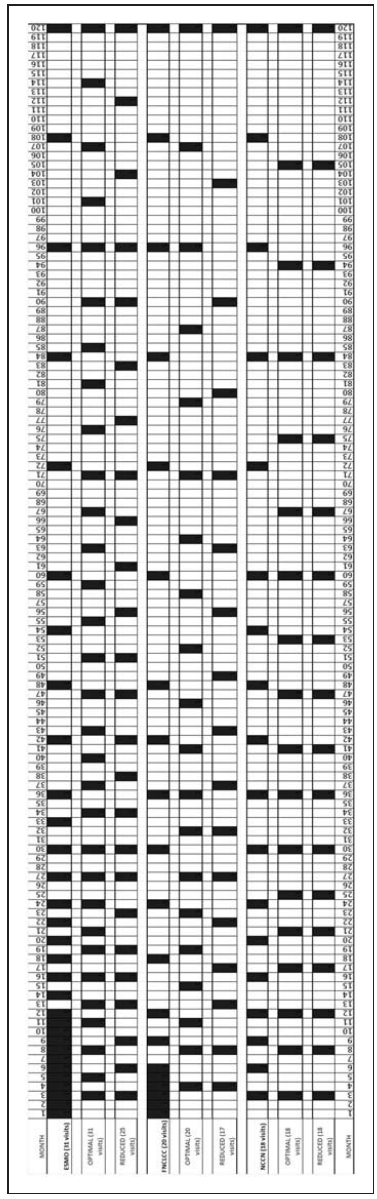

Figure 3. Visits scheduling according to the different follow-up calendars.

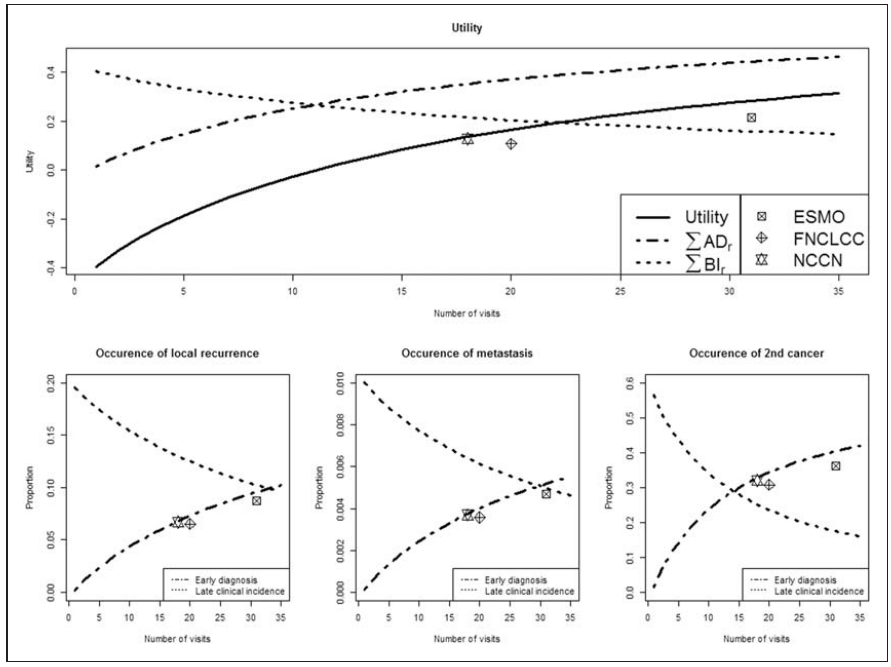

Figure 4. The graph at the top shows the evolution of the optimal utilities and the probabilities of cure. The different points represent the utility function of the schedules recommended by the three scientific societies. The three graphics at the bottom represent the evolution of the proportion of early diagnosis and late clinical incidence by number of scheduled visits for each recurrence type. The corresponding proportions of early detection of relapses are pointed for each recommendation.

ESMO: European Society of Medical Oncology; FNCLCC: Fédération Nationale des Centres de Lutte Contre le Cancer; NCCN: National Comprehensive Cancer Network

The cost of the surveillance is strongly related to the total number of visits. If unit costs of the follow-up visits were known, we could estimate the realized savings by optimizing the follow-up.

5 Discussion

Using this natural history Markov model, the proposed method provides the probability of detection of a recurrence at asymptomatic phase at a scheduled visit and the one of onset of symptoms between two consecutive visits. The utility function is designed to sum up all these probabilities. This is an extension of the optimal screening method proposed by Zelen.[13] As it distinguishes the natural history of the different types of relapses the patients are at risk of, it is adapted for post-therapeutic follow-up where these relapses have different distribution functions.

Finally, the method can be used for any cancer, regardless to the localization. It can even be extended to other cases were the need of post-therapeutic surveillance is important (e.g., transplantations).

The comparisons of the optimal schedules provided by the model with the strategies proposed by different scientific societies show the efficacy of the tool. The optimization increases the number of patients who will be early detected and decreases the number of patients who will transit to late stage. Otherwise, death has not been considered among competing events. The model also does not handle the probability of cure. These might lead to a slight overestimation of the probabilities of relapse.

One of the advantages of the optimization method is that it permits a diminution of the total number of visits to be undertaken by the health facility. This approach will need fewer resources. Hofmann et al.[27] has identified three different costs in case of follow-up. The unit cost of a follow-up visit where no relapse is detected, the cost of positive visits when relapse is diagnosed, and the cost for visits where false positive results are obtained. The estimation of the different costs implies assessing the different exams to be done for each visit type and determining the unit cost of each of them. Filleron et al.[25] have then shown how costs could be used as criteria to determine an optimal follow-up schedule.

Some alternative methods have been proposed in the literature. Zelen has proposed to plan the follow-up visit when the probability of occurrence of a recurrence reaches a threshold value.[13,18,40] This method does not need any weighting coefficient for the definition of a utility function. However, it depends on the arbitrary choice of the threshold value. Instead of using a Markov assumption to model the natural history of the disease, Pinsky[41] proposed a convolution model. This approach should provide more accurate estimations of the incidence of early and late stages of relapses. Its application will however need a lot of information about the recurrence distribution function and is more complicated in practice. The natural history of the relapse could also be modeled in more different states, including carcinogenesis and late preclinical stage,[42] including nodal values[9,12] or including over detection.[43] This will provide more flexibility to the estimation, but the model will be less parsimonious and more difficult to maximize.

One of the major assumptions of the model is that it does not allow transitions between different types of recurrences. A model which allows such transition could be of more interest for clinicians as it could program follow-up schedules to ensure intervals long enough that there were sufficient preclinical local recurrences to detect to render the activity cost-effective, but short enough to minimize the likelihood of distant metastases. Taking into account the possibility of having several recurrence types in the same time frame should permit a better planning to focus on given recurrence types.

The natural history proposed model assumes a homogeneous regular Markov distribution, which is a strong assumption. In fact, the hazard of a recurrence could vary with time. Moreover, the transitions to a preclinical state depend on the probability distribution in the preclinical state and the transition intensity from the preclinical to the clinical state.[14] This hazard could also depend on some individual characteristics. All the patients do not need to be followed up by the same scheme. The follow-up should be tailored to fit the individual characteristics.[44] So for each group of patients, the corresponding recurrence distribution parameters should be estimated. These individual characteristics can be used to estimate tailored lengths of surveillance.[31] The number of visits could then be refined in order to obtain equivalent maximal utilities.

Additionally, the coefficients of the utility function are considered as fixed. However, if A_k and B_k are the prognosis in case of a recurrence of type k, these could depend on the time since the end of the treatment. They could also depend on the individual characteristics of the patients.

Another limitation of the proposed model is that it is based on previous estimations. In fact, the determination of optimal schedules requires previous information on the transition intensity for the healthy state to the preclinical state of any relapse type and also from the preclinical state to the clinical one. These data are not always available for the different cancer locations as they may vary according to the countries, to the health care systems, etc. Finally, this could make the method difficult to apply in many cases. If observed data are available, it is also possible to construct a likelihood function and to estimate the parameters empirically. Similar works have been performed in the case of screening programs.[45]

A possible extension of the approach will be to design it with a dynamic model. The health situation of a patient may evolve during his follow-up, and he may move from one group to another. In this case, his surveillance strategy should adapt to this evolution. So the models underlying the follow-up schemes should be able to include this additional information. This is one of the properties of the delayed Markov model proposed by Özekici and Pliska[10] or the stochastic differential equations provided by Veestraeten.[46]

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Chapitre IV

Algorithme d'évaluation de la surveillance

I Problématique

Plusieurs calendriers de suivi sont proposés par des sociétés savantes. Ces directives sont principalement caractérisées par leur faiblesse en termes de preuves scientifiques [40]. En effet, l'approche recommandée pour l'évaluation d'une stratégie de surveillance dans le cadre d'une approche de médecine probante serait la mise en œuvre d'un essai clinique randomisé. Par ailleurs, mettre en œuvre des procédures de suivi moins intensives que celles recommandées pourrait présenter des problèmes d'éthique [80, 81]. Il est alors nécessaire de définir une autre stratégie pour évaluer dans un premier temps un calendrier de surveillance post-thérapeutique et pour comparer plusieurs calendriers afin de permettre une évolution des méthodes et pratiques.

Des développements théoriques ont été proposés pour l'évaluation des stratégies de dépistage du cancer. Davidov et Zelen [82] ont défini un cadre stochastique pour la conceptualisation de telles évaluations pour le dépistage du cancer du sein. Par suite Hu et Zelen [83, 84] ont discuté des obstacles rencontrés dans ces évaluations. Enfin, Kafadar

et Prorok [85] ont décrit un algorithme de simulation d'un essai clinique permettant d'évaluer un programme de dépistage. Il est par contre difficile de trouver une telle littérature dans le cadre du suivi des patients à la suite de leur traitement. Alors que la nécessité de telles approches est régulièrement relevée, les approches méthodologiques sont inexistantes. Il est donc nécessaire de proposer une méthodologie pour évaluer les calendriers de surveillance avant de proposer un essai randomisé.

II Objectifs

L'objectif du chapitre est de proposer un algorithme qui reproduirait un essai clinique permettant d'évaluer une stratégie de surveillance en utilisant les outils de simulation numérique. Au vu des critères de jugement, il sera possible d'évaluer la non-infériorité d'une stratégie moins contraignante par rapport à une organisation qui serait la pratique courante.

III Méthodes

III.1 Description du modèle

L'approche proposée est basée sur un modèle à cinq états. L'état initial représente la phase « Sain » où le patient, à la sortie de son traitement, ne présente plus de tumeur ou est dans une phase où sa tumeur serait indétectable. Deux types de récidives sont ensuite considérés. La récidive loco-régionale et la métastase à distance. L'hypothèse d'un traitement curatif en cas de métastase est considéré comme nul dans notre cas. Un patient en phase de rémission est à risque de passage direct en phase de métastase. Il s'agit de la métastase primaire. De plus, lorsque le patient a développé une récidive loco-régionale, il a, en plus du risque de métastase primaire, un risque de développer une métastase secondaire, qui est plus important. La récidive loco-régionale est considérée en deux états distincts : un état de récidive en phase pré-clinique et un état de phase clinique de la récidive. Enfin, le dernier état de l'histoire naturelle est le décès. Tous les patients sont à risque de décès de causes diverses. De plus, les patients, lorsqu'ils développent une métastase, sont à fort risque de décès du cancer.

Les hypothèses suivantes sont donc retenues :

- les décès du cancer sont dus aux métastases ;
- le risque de métastase primaire et le risque de décès d'autre cause sont constants tout au long de l'histoire du patient ;
- l'apparition d'une récidive loco-régionale accroît significativement le risque de métastase (métastase secondaire) ;
- la phase clinique de la récidive loco-régionale aussi bien que la métastase sont irréversibles.

III.2 Approche par simulation

L'essai clinique à simuler est un essai randomisé de phase III avec deux bras parallèles. Un bras correspondant au rythme de suivi expérimental est comparé à un bras standard qui correspond au rythme de suivi couramment utilisé. Le critère d'intérêt principal est la survie globale. La survie spécifique est considérée comme critère d'intérêt secondaire.

Les principes de modélisation dynamique des transitions [86] sont appliqués pour la génération des histoires de la maladie des patients. La simulation est effectuée au moyen de simulation des événements discrets [87, 88]. Enfin la stratégie adoptée est orientée patient [89].

L'histoire de vie est d'abord générée pour chaque patient suivant les hypothèses de la maladie et de la population à étudier. Les dates de transition entre les différents événements sont générées. Cette génération est effectuée selon le principe de l'histoire naturelle, sans aucune intervention. Les informations produites pour chaque patient sont ensuite soumises au calendrier de surveillance auquel celui-ci est affecté. L'algorithme teste la capacité de ce calendrier à programmer une visite alors que le patient est dans la phase pré-clinique d'une récidive loco-régionale et à détecter celle-ci. Lorsque la récidive est détectée, l'histoire de vie est modifiée afin de prendre en compte le traitement reçu. La date de l'événement final, à savoir la date de décès, est enregistrée.

L'approche proposée présente plusieurs avantages. Tout d'abord, elle offre une grande flexibilité dans la génération des histoires de vie. Elle n'est pas contrainte par des hypothèses stochastiques telles que celles de Markov [90]. Les délais de transition peuvent être indépendants ou fonction de l'histoire passée. Ils peuvent être homogènes ou à risques

variables dans le temps. Ils peuvent aussi être fonction d'autres facteurs individuels, environnementaux, etc. De plus, l'utilisateur peut définir sa population par rapport à l'objectif de son évaluation. Il peut reproduire l'essai pour une population âgée, féminine, ou présentant d'autres critères spécifiques. Il peut prendre en compte des facteurs divers tels qu'un effet de groupe dans le cas d'un essai multicentrique. Le nombre de sujets nécessaires ainsi que la durée totale de l'étude (durée d'inclusion et période d'observation) sont définis en s'adaptant aux situations réelles.

Plusieurs autres paramètres pourraient être pris en compte dans le modèle afin de s'adapter aux situations réelles. A ce titre, l'algorithme :

- prend en compte les patients perdus de vue,
- s'adapte à l'observance des calendriers de surveillance,
- s'adapte à la sensibilité des examens de suivi,
- s'adapte à l'efficacité du traitement proposé à la récidive,
- etc.

Finalement cette approche peut être considérée comme un important outil de décision pour évaluer toutes les phases d'une stratégie de surveillance post-thérapeutique.

IV Article : Algorithme de simulation

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An Algorithm to Evaluate Follow-Up Strategies after Primary Treatment in Oncology by Computer Simulation

Running title: Algorithm evaluating cancer follow-up.

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ABSTRACT

Organizing the surveillance of patients treated for cancer, for early diagnosis of recurrences, is still a subject of debate. Evidence needs to be highlighted to determine when a particular follow-up strategy is efficient enough to have a significant impact on survival. However the clinical evaluation of follow-up programs after primary treatment is difficult to undertake. This paper proposes an algorithm to evaluate a novel follow-up surveillance strategy after treatment in oncology. A computer based randomized two parallel arms non-inferiority clinical trial is proposed to compare two strategies. Overall survival and cancer specific mortality were the two endpoints evaluated. The methodology of Discrete Events Simulation, based on Patient Oriented Simulation Technique, was used. The natural history of the patient's disease after primary treatment was generated for each individual. Then, for each scheduled visit date, this history could be modified if a relapse was detected early enough and efficient treatment options are available. An application of the algorithm based on breast cancer data shows its advantages in decision making.

Key words: Cancer Surveillance; Follow-Up; Early diagnosis; Loco regional recurrence; Algorithm; Discrete Events Simulation; Patient Oriented Simulation Technique.

1 INTRODUCTION

After curative treatment for cancer, patients are at risk of different event types such as loco-regional relapse, distant metastasis, and second primary cancer. Scientific societies have put forward recommendations to organize follow-up for these patients, after their primary treatment. The main objective of this follow-up phase is to detect relapses or second primary cancers early enough in order to propose curative treatment. For example, after a treatment for primary breast cancer, the American Society of Clinical Oncology (ASCO) recommends physical examinations every 3 to 6 months for the first 3 years, then every 6 to 12 months for the next two years and then annually (1). The schedules proposed by other societies after primary breast cancer are not very different (2,3). However, evidence of the efficacy of these surveillance schedules is still lacking (4,5). The recommended calendars are mostly based on expert advice.

Post-surgery, -chemotherapy or -radiotherapy surveillance is supposed to be valuable when it permits the increase of life expectancy and the improvement of quality of life. As patients are expecting higher quality care, and governments and health care providers are oriented to control their spending, the strategies need to be optimized. One aspect concerns the focus of new strategies on the detection of potentially curable events. The idea of optimizing the surveillance schedule has been discussed in several works (7–11). The literature produces more and more follow-up strategies which need to be compared in order to evaluate their efficacy. One possible solution is to compare different surveillance programs by a randomized trial. Such a trial would only be possible if both patients and physicians observe the protocol during a long period, which demands important financial and logistical costs. Then, less intensive procedures could be considered as non-ethical unless clear evidence is provided that their efficacy is comparable (12,13). Fishman (14) has defined computer simulation as a sampling experiment carried out by a computer. Burton (15) proposed a methodology to design such studies in medical research. These have been used in the literature to evaluate or to compare screening programs(16–19). Kafadar and Prorok (20) have proposed procedures and algorithms to perform a cancer screening study. Other simulation studies were done for surveillance(12,21–23).

The main objective of this paper is to propose an algorithm to perform a computer simulation study to compare surveillance strategies in oncology after primary treatment. The defined method is consistent with the recommendations of the ISPOR-SMDM Good Research Practices in Modeling Task Force-3 (24) on states transition modeling. It also uses the Discrete Events Simulation (25) approach accordingly to the recommendations of the ISPOR-SMDM Good Research Practices in Modeling Task Force-4 (26). The simulation is performed using the Patient-Oriented Simulation Technique (POST) (27). Section 2 describes the proposed methodology. This approach is applied to evaluate a follow-up recommendation for breast cancer in section 3. The presented tools are discussed in section 4.

2 METHODS

2.1 DISEASE NATURAL HISTORY

After curative treatment for cancer, patients are at risk of different events types: loco-regional relapse, second primary cancer, distant metastasis or death. For simplification purposes, a model with two different event type, recurrence and death, is treated in the present paper. This can be generalized to more event types once data about the transition processes are available.

The natural history of a patient after curative treatment of cancer can be modeled in five states (Figure 1). Patients are considered at risk of death from causes other than cancer. Patients, while they are alive, are also considered at risk of metastasis, which is one of the most common causes of death from cancer (28). The prognosis for cure after a metastatic event is poor for most cancer sites (29–31) and life expectancy is limited (32). A patient in a remission phase is also at risk of a local recurrence (LR) from his cancer. Three phases are considered for the local recurrence. The first phase is the early stage of LR, where the patient is in an asymptomatic stage. This is also called the preclinical stage of the relapse. The second phase is the symptomatic stage of the recurrence, also called clinical stage. The prognosis of cure for a patient in clinical stage of local recurrence is considered poor while this prognosis could be better when the patient is still in an asymptomatic phase. Having a local recurrence then increases the risk of occurrence of distant metastases (33). The occurrence of a metastasis due to a recurrent tumor is called secondary metastasis. Finally death from cancer most often occurs after metastasis.

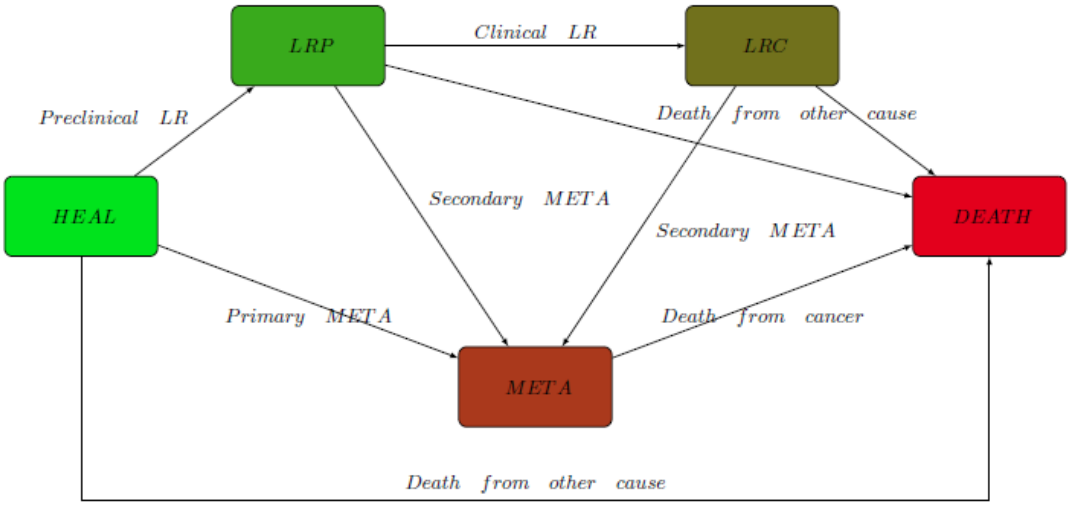

FIGURE 1: 5 states model for surveillance

2.2 HEALTH STATE DEFINITIONS

HEAL is the state corresponding to total remission. The patient enters this stage at the end of the acute phase of curative treatment.

LRP represents the preclinical (asymptomatic) stage of a local relapse while **LRC** represents the clinical (symptomatic) stage. Patients move naturally from **HEAL** to **LRP**, then **LRC**.

META represents the distant metastasis stage. Patients in **HEAL**, **LRP** or **LRC** stages are considered at risk of primary metastasis. Secondary metastases can also be observed for patients in **LRP** and **LRC**. Thus, patients in **LRP** or **LRC** stage are at risk of two types of metastases.

DEATH represents the final absorbing state which is death. Patients in any stage are at risk of death from any cause. Patients in **META** stage are additionally at risk of death from cancer.

The aim of post-therapeutic follow-up is early diagnosis of loco-regional recurrence (i.e. in preclinical phase), that is to detect a patient early enough after his transition from **HEAL** to **LRP** before he transits to **LRC** or **META**. If a recurrence is detected early enough, a treatment with curative intent can be undertaken. The objective of this treatment is to prevent any transition to **LRC** and to reduce the risk of transition to **META**.

2.3 THE APPROACH FOR SIMULATION

A computer based randomized two parallel arms clinical trial should be proposed to compare a new follow-up strategy to a reference one. Patients may be randomly allocated to one arm at their exit of curative treatment for cancer. The main objective defined for this trial would be to compare two follow-up programs using overall survival as the primary endpoint. Cumulative incidence of death related to cancer would also be evaluated as a secondary endpoint.

The disease history of the patients included in this trial is simulated through a Discrete Events Simulation (DES) Method, which is a computer-assisted modeling methodology designed to capture flow time, competition for resources and the interdependency of events providing insight into the simulated system dynamics (34). It is a micro-simulation in which the individual outcomes (realistic simulations of patient histories) are generated in such a manner as they move through a system, participate in different processes and consume resources (35). Events occurring to patients and how they interact with each other, with the health care system and with the general environment, can be modeled simultaneously (26). The patients are followed as they pass through different health states and different output measures needed to evaluate the system behavior are calculated. This approach is more flexible than the Markov related processes encountered in most of the modeling techniques to evaluate a health care technique (35,36).

2.3.1 GENERATION OF THE KEY DATES

The simulation program generates time intervals between all two by two consecutive states, for each patient. These simulations are performed according to the specific assumptions for the cancer site, the

patients' characteristics and other important prognostic factors. The time spent in a given state can be dependent or not on the time spent in the previous one. For example, the sojourn time in secondary metastasis state can be a function of the time spent in the local recurrence state. Once the time intervals are generated, the program computes the key dates of the disease history of this patient:

- The date of inclusion in the trial t_0, generated within a defined inclusion period, represents the date the patient enters the state **HEAL**.
- The date of the end of the trial is T; all the patients who are alive at this date are considered as censored observations.
- A date of loss to follow-up *c* is generated for censored patients, where $c \leq T$.
- A date of death from cause other than cancer *d* is generated for a possible transition **HEAL → DEATH**.
- A date of appearance of primary metastasis *pm* is generated for a possible transition **HEAL → META**.
- A date of appearance of local relapse in preclinical stage *sp* is generated for a possible transition **HEAL → LRP**
- A date of appearance in clinical stage of local relapse *sc* is generated for a possible transition **LRP → LRC**.
- A date of appearance of secondary metastasis sm_p is generated for a possible transition **LRP → META**.
- A date of appearance of secondary metastasis sm_c is generated for a possible transition **LRC → META**.
- Finally the date of appearance of secondary metastasis is defined as $sm = min(sm_p, sm_c)$ and the date of appearance of a metastasis is $met = min(pm, sm)$.
- A date of death from cancer *dc* is generated for a possible transition **META → DEATH**.
- Finally the date of death is defined as $de = min(d, dc)$ and the date of the last contact with the patient or death is $z = min(de, c)$.

The follow-up strategy applied to a given patient *i* in his randomization arm are given dates where follow-up clinical visits and examinations are scheduled. The schedules are characterized by the total length of the surveillance and the time between each pair of consecutive visits. Let *n* be the number of visit dates of a given calendar. Let $t_{ir}, r = 1, \ldots n$ be these visit dates with $t_{i0} < t_{i1} < \ldots < t_{ir} < \ldots < t_{in}$, where t_{i0} is the date of inclusion for patient *i*. The program evaluates the patient at each of these *n* visits.

2.3.2 HANDLING THE ADHERENCE TO THE SURVEILLANCE

The first step of the evaluation is the adherence to the follow-up schedule. A patient could miss a given appointment for a follow-up visit. This non-adherence can be completely random or related to the surveillance schedule. Patients could be more likely to miss visits when they are, for example, too close or too numerous or when the follow-up period is getting longer. The program evaluates the

adherence of a patient i at the visit r by generating his presence according to a Bernoulli distribution with a probability η_r . Constant η implies completely random adherence. Alternatively, the η_r can be generated according to a specific process used in the assumptions. At each increment of the program (visit date t_{ir}), the effectiveness of the visit is generated as a binary value with the probability η_r . If this value is null, then the program moves to the following visit date, t_{ir+1} . If the value is one, then the exact date of the visit is imputed.

The second aspect of the adherence concerns the delays to the appointment dates, in order to generate the exact date when the examinations will be performed. A patient could come a few days before or after the theoretical date of the visit. Finally, when the r^{th} visit of the patient i is held (with a probability η_{ir}), the exact date of visit will be $t^*_{ir} = t_{ir} + \varepsilon_{ir}$, were ε_{ir} is generated by a random distribution with a null expected value. Assumptions can be made about the value and the homogeneity of the variance of ε_{ir}. One could consider that the patient will be closer to the schedule in the period following the end of the treatment and will have larger delays with the time, implying increasing variance with *r*. The distribution of ε_{ir} will be right skewed if the patients are considered to be more likely to come after the scheduled date of visit or left skewed if the patients are considered to be more likely to come before the scheduled date. The values of ε_{ir} can also be generated according to the patient's characteristics such as age, the accessibility to the health facility or eventual disabilities.

2.3.3 TESTING TO DETECT PRECLINICAL STAGE LR

When a patient comes for a visit, he may be in one of the four following states: **HEAL**, **LRP**, **LRC**, **META**. If he is in the **HEAL** state, the examinations could not detect anything. The program moves to the following visit. If the patient has reached the state **LRC** or is already in a state **META**, it is assumed that this will be detected after the clinical examination. Then the surveillance schedule will be interrupted because it failed to detect a **LR** in a preclinical phase. So the patient exits the program. Finally, if a patient comes for a visit while he is in a preclinical phase of **LR**, that is **LRP**, the following evaluations are performed.

Clinical and radiological examinations are performed in order to detect an eventual **LRP**. However, these are generally not 100% sensitive. A patient in **LRP** stage could have visits where the exams fail to detect his recurrence. Let β be the sensitivity of the visit examinations. The program generates a binary value with probability β. If the value is null, the recurrence is not detected and the patient is scheduled for the following visit. If it is one, the patient is detected to be in **LRP** state. Then he will be subject to a potential curative treatment.

2.3.4 GENERATION OF THE EFFECTS OF THE TREATMENT AFTER PRECLINICAL LR

The treatment after a preclinical LR aims to reduce the risk of distant metastasis. If it is started early enough, the patient will not move to a clinical stage. Thus, for a patient properly diagnosed in **LRP**, the date of transition to **LRC** is sent to infinity ($sc = \infty$). The curative treatment will also tend to eliminate

or to reduce significantly the risk of secondary metastasis. This will postpone the date of occurrence of secondary metastasis which was $sm=min(sm_p;sm_c)$ to $sm=sm_p$ as $sm_c = \infty$.

2.3.5 PROGRAMING AND SENSITIVITY ANALYSIS

The simulation methodology has been computed using R software (37). A sensitivity analysis was performed to assess the importance of the effect of the treatment after local recurrence. One extreme hypothesis will be to consider that patients in preclinical phase of local recurrence have the same hazard rate of metastasis as patients without recurrence. Alternatively, one could consider that patients with local recurrence in preclinical phase have an additional hazard rate of secondary metastasis. This hazard rate could be comprised between zero and the hazard of a secondary metastasis in case of clinical state of local recurrence. A one way sensitivity analysis was performed to determine an adequate value of this hazard rate. The simulation program was run for 1,000 patients 500 times for hazard of secondary metastasis during local recurrence in preclinical stage from 0 to 9 times the hazard rate of primary metastasis.

Another sensitivity analysis was performed to ensure the sensitivity and the robustness of the method according to two parameters. The purpose was to check the evolution of the principal outcome according to two principal characteristics: the sensitivity β of the follow-up exam and patients' adherence η to the program. Concerning the first parameter β, it varied from 1 assuming no detection fails to 0 for all the exams and all the patients. For the second parameter, constant probabilities were tested with time for all patients with values of η varying from 1 to 0 for absolutely no adhesion to the surveillance. The program was run for a simulation of 1,000 patients 500 times for a sequence of values for β from 0 to 1 by 0.1 and for a sequence of values for η from 0 to 1 by 0.1.

2.4 VALIDATION OF THE METHOD

Two validation processes were used for the method according to the recommendations of the ISPOR-SMDM Modeling Good Research Practices Task Force 7 on Model Transparency and Validation (38). The first one is the face validity which consists in the validation of the model structure, the data source and the problem formulation principally by literature sources and experts recommendations. The face validation concerned the generation of time to event, the adherence to the guidelines, the sensitivity of the tests and the effect of treatment after early detection.

Several studies discussed the time before recurrence after a primary treatment. Boag (39) has proposed a cure model which is a mixture of a binomial and a lognormal model. Some generalizations of this approach were then proposed (40–42) using Weibull, log-logistic functions or including frailty. The case of several recurrence types was then studied using competing risks (43–46). Finally, some assumptions were made to model the patient's history of disease using multistate approach (21,47).

In the case of colorectal cancer, Salz et al. (48) have found in their cohort in the United States that 51% of the patients did not receive any colonoscopy within 14 months after surgery. They have highlighted some related factors such as the type of cancer, the visit to a primary care physician,

adjuvant chemotherapy and comorbidities. Lafata et al. (49) have shown some sociodemographic factors to this adherence. The adherence to the follow-up guideline should also depend on the type of exams. Körner et al. (50) have found higher adherence rates of 55% for colonoscopy and 85% for ultrasonography of the liver in Norway, for example. We have not found any resource in the literature dealing with the lag for a planned follow-up visit. However, experience has shown that patients sometimes come to the visits with some delay.

Several papers discussed the sensitivity and specificity of cancer screening tests. In the case of breast cancer, Ravert et al. (51) discussed these indicators in a literature review. The sensitivity of mammography was ranged from 0% to 77.6% while the specificity lied between 62.5% and 99.5%. The sensitivity of ultrasonography was from 13% to 100% and the specificity from 77.5% to 96.8%. Finally, the sensitivity and specificity of breast magnetic resonance imaging (MRI) were ranged respectively from 77% to 100% and from 59.4 to 95%.

The effect of the treatment on life expectancy was more difficult to model. Jacobs (21) assumed that after detection of a recurrence, the patient returns to the initial state with a given probability. This approach was also used by Ritoe (52). Then, when a recurrence is detected, the patient has this given probability to be completely cured. A patient curatively treated after a recurrence is then at risk of the modeled events of the initial post-therapeutic stage, regardless to his previous history, according to the Markov assumptions. Such an approach is easy to model but, according to expert's observations, one cannot consider that the history of life of a patient is memoryless. The compromise we found between programmability and applicability of our model was to consider that the patient had a risk of developing metastasis increased first by having a recurrence in asymptomatic stage and that the risk was even higher when the recurrence occurs in the clinical stage. However, when the recurrence was detected, the proposed treatment just blocks the acceleration of the metastatisation (53).

The second validation process was verification of the programming code. All the programs were written by the first author and validated by the second and the last author of the paper.

3 APPLICATION

3.1 THE QUESTION OF FOLLOW-UP AFTER A TREATMENT FOR BREAST CANCER

Despite the lack of evidence of post-therapeutic follow-up improvement on survival or life expectancy, routine surveillances are still used for patients treated for breast cancer. In the GIVIO trial (54), 1,320 women were observed prospectively after their treatment. 655 received intensive follow-up which included physician visits, and performance of bone scans, liver sonograms, chest X-rays and laboratory tests at predefined intervals. The 655 other patients were seen by their doctors at the same frequency but only clinically motivated tests were performed. No significant difference was found for overall survival between both groups. Both studies were published twenty years ago. The therapeutic solutions have changed a lot since then and are still evolving. Then the usefulness of follow-up should have changed during the last ten years. It is important to have a specific tool which will help updating the patients care policy. This tool needs to be less restrictive than a clinical trial on ten years. Finally, a program which will perform such clinical trials by computer based simulation can help to monitor the evolution of the follow-up schedules according to the changes in treatments.

3.2 DATA SOURCE

Two theoretical populations were considered for the application of the method. A low grade population of women treated for breast cancer and a high grade population. Data concerning the risk of ipsilateral breast tumor recurrence and distant metastasis were calculated with two web tools, IBTR! and Adjuvant!. IBTR! (55) permits the estimation of the risk of loco-regional recurrence after 10 years according to some prognosis factors. Adjuvant online (56) is a decision making tool for health care professional, using information on the Surveillance, Epidemiology and End Results (SEER) database in the United States of America.

The women were simulated according to the following characteristics: 53 years of age, all node negative, tumor size of 1.5 centimeters, unknown margin estrogen receptor lymphovascular invasion status. The patients were not treated by chemotherapy, by tamoxifen/aromatase inhibitor nor by radiotherapy. Low grade patients were considered in low risk group with tumor grade 1 and high grade patients were in high risk group with tumor grade 3. The estimated risk of local relapse before 10 years was 4.9% for low grade patients and 10.6% for high grade. The overall risk of recurrence were respectively 13.0% and 40.0%, leading to a risk of metastasis respectively of 8.1% and 29.4%, according to the study hypotheses.

The sojourn time in preclinical state of local recurrence before moving to a clinical state was estimated in the literature at an average value of 2.8 months (57). The patients experiencing a local recurrence are at risk of secondary metastasis. Engel et al. (53) and De Bock et al. (58) have estimated the risk of metastasis after a local recurrence as three times the risk of primary metastasis.

Survival time was estimated according to the age specific life expectancy of the female population of the United States of America (59). The life expectancy for women aged 50-54 was estimated to 33.12 years. Hatteville et al. (60) have estimated that the life expectancy of patients with distant metastases after breast cancer was divided by 69. This assumption is used to simulate time to death from cancer, after the onset of metastasis.

Our simulation program was written in order to ensure enough flexibility. Times between two consecutive events were generated according to a cure model as a mixture of a binomial and a Weibull distribution (39,61). According to the assumptions, for the following applications, times to events were all generated with constant hazards and without cure rates. The date of loss to follow-up was also generated following an exponential distribution with a mean value of 35 years.

A hypothetical delay was considered around each scheduled appointment date as mentioned in section 2.3.1. The difference between the scheduled appointment date and the real date of visit was generated following a beta centered and right distributed variable with a variance 0.012.

Finally the different parameters were generated as shown in table 1.

TABLE 1: Generation of the values for the application example

Generated value	Formula expression	Description
Date of inclusion	$t_0 \sim Unif(0;12)$	Uniform distribution within 0-12 months;
Follow-up time	$T = 120$	Maximum follow-up time of 120 months;
Date of loss of follow-up	$c \sim min(t_0+Exp(420),T)$	Exponential distribution with mean 1/35 years, bounded by *T*;
Time before death from other cause	$d \sim Exp(397.44)$	Exponential distribution with mean 1/33.12 years (62) ;
Time before primary metastasis	$pm \sim Exp(1420.64); Exp(344.69)$	Exponential distribution with mean 1/118.38 and 1/28.72 years for low grade and high grade patients respectively (59) ;
Time before local recurrence	$sp \sim Exp(2388.47); Exp(1070.96)$	Exponential distribution with mean 1/199.04 and 1/89.24 years for low grade and high grade patients respectively (58) ;
Time in preclinical state of local relapse	$sc \sim Exp(2.80)$	Exponential distribution with mean 1/0.23 years (60) ;
Time before secondary metastasis in preclinical state	$sm_p = +Inf$	The treated patient will not have (56) ;
Time before secondary metastasis in clinical state	$sm_c \sim Exp(2.80/3)$	Exponential distribution with mean 1/0.08 years (56) ;
Time in metastasis state before death from cancer	$dc \sim Exp(397.44/69)$	Exponential distribution with mean 1/0.48 years (63) ;
Probability of attendance to the visit r	$\eta_r=1; r$	The patients respect all the visit schedules ;
Delay from the date of visit	$\varepsilon_r \sim Beta(1,7)-0.125$	Centered and right distributed beta variable.

3.3 FOLLOW-UP SCHEDULES AND NUMBER OF PATIENTS

The National Comprehensive Cancer Network (NCCN) guidelines (2) for follow-up after a treatment for invasive breast cancer are one of the most observed recommendations. They recommend history and physical exam every 4-6 months for 5 years then every 12 months and mammography every 12 months. These recommendations are consistent with the recommendations of the American Society of Clinical Oncology (ASCO) (1) and the European Society of Medical Oncology (ESMO) (3). For

simplification purpose, all the scheduled visits are considered as equivalent (i.e. the same examinations are done for all the visits). Then, the lightest form of the schedule will be considered (one visit every 6 months for 5 years then 1 visit yearly), leading to 15 visits in 10 years. The recommended follow-up schedule is compared here with the absence of follow-up.

Ten years death rates were estimated to 29% and 43% respectively for low and high grade patients in the standard arm, which refers to patients followed according to the NCCN guidelines, from a large simulation on 50,000 patients. The non-inferiority hazard ratio margin was defined as a hazard ratio of 0.85. To conclude to non-inferiority (i.e. reject the null hypothesis), the lower bound of the 95% confidence interval resulting from the comparison between the two arms should be greater than this specified margin (62). With a type I error of 5% and 90% power, a total of 1,290 events were required for both groups, leading to an initial sample size estimate of 4,500 patients (resp. 3,000) in the low risk group (resp. high risk) (63).

3.4 POPULATION CHARACTERISTICS

In this section, one run of the simulation is presented to observe the characteristics of the women. 2,250 patients with low grade and 1,500 patients with high grade were included in each study arm. These populations were followed for 10 years. Table 2 presents the obtained results for this trial. 20% of the low grade patients and 18% in the high grade group of the patients were lost to follow-up before the end of the study.

TABLE 2: Description of the 2 simulated study populations

	Low Grade		High Grade	
FU schedule	**Recommended**	**No follow-up**	**Recommended**	**No follow-up**
Number of patients	2,250	2,250	1,500	1,500
Number of deaths	627	652	645	643
Lost to follow-up before T	460	454	564	278
Total number of visit	27,869	-	16,683	-
Number of LR	81	76	110	116
Number detected LR	30	-	39	-

In the low grade patients' trial, 81 women included in the recommended follow-up arm had LR while 76 LR were observed in the second arm. The follow-up schedule detects 30 relapses in an asymptomatic stage. In the high grade cancer women group, 110 recurrences were observed in the recommended arm and 116 in the no follow-up study arm. The NCCN follow-up could detect 39 recurrences in preclinical phase. However the simulated total numbers of visits for this follow-up are 27,869 and 16,683 for the low and high risk group respectively. Finally 652 low grade patients who were not followed died. 627 patients followed according to the NCCN guideline died. The number of deaths for high grade patients was 645 for NCCN follow-up and 643 for no follow-up.

Figure 2 presents the evolution of the probability of death for the 10 first years. Patients treated for low grade cancer are more at risk of death from other cause while the patients treated for high grade

cancer have more important risk of death from cancer. Estimated hazard ratios for overall death while recommended follow-up was undertaken compared with death without follow-up were 0.94 (95% CI 0.85-1.05) for low grade cancer patients and 1.02 (95% CI 0.92-1.14) for high grade cancer, which shows no statistical difference between the two arms. Graphics show that death from cancer is slightly more important when patients are not followed after their treatment. The difference is less important when patients were treated for high grade cancer. However, no difference can be highlighted for overall death. Estimated sub distribution hazard ratios for death from cancer with a competing risk of death from other cause were 0.85 (95% CI 0.70-1.05) and 0.96 (95% CI 0.83-1.11) for low grade and high grade cancer patients respectively, leading one again to no statistical difference in the two arms.

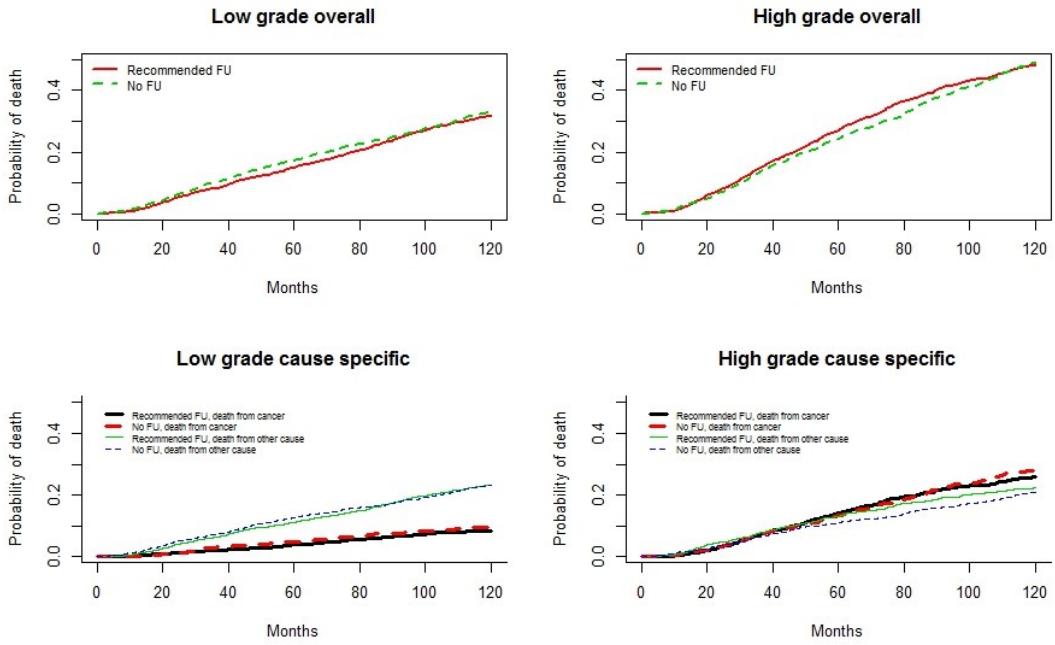

FIGURE 2: Probability of death for low grade and high grade patients for one run of the simulation

3.5 OVERALL SURVIVAL AND CANCER SPECIFIC MORTALITY

The results of the simulation from 1,000 samples are presented in table 3. The median number of performed visits were 20,843 (IQR 247) and 13,359 (IQR 211) for low grade and high grade patients respectively. For the low grade patients a median number of 59 (IQR 10) local recurrences occurred of which 19 (IQR 6) were detected in the preclinical stage. The number of local recurrences for high grade patients was more important (median 80 and IQR 11) and a median number of 26 recurrences (IQR 7) were detected in the preclinical stage.

TABLE 3: Characteristics of the simulation on the recommended follow-up schedule simulated for 1,000 samples

	Low Grade			High Grade		
	Number of visits	Number of LR	Number of detected LR	Number of visits	Number of LR	Number of detected LR
Min	20,129	38	5	12,878	50	13
Quantile 25%	20,724	54	16	13,257	75	23
Median	20,843	59	19	13,359	80	26
Quantile 75%	20,971	64	22	13,465	86	30
Max	21,387	82	31	13,841	111	48

The estimated hazard ratios are defined as the ratios between the hazards of death for NCCN follow-up arm and the hazards of death for the no follow-up arm (Figure 3). The 2.5% quantile of the Cox hazard ratio of overall death between no follow-up schedule and NCCN schedule was 0.87 for low grade patients and 0.85 for high grade patients. Thirteen simulated samples of low grade patients and 19 simulated samples of high grade patients presented hazard ratios smaller than 0.85. Then the 5% percentile was greater than this reference value, confirming the hypothesis of non-inferiority. The observed median values of the hazard ratios were 0.96 (IQR 0.93 – 1.00) and 0.95 (IQR 0.92 – 0.99) for low grade and high grade patients respectively.

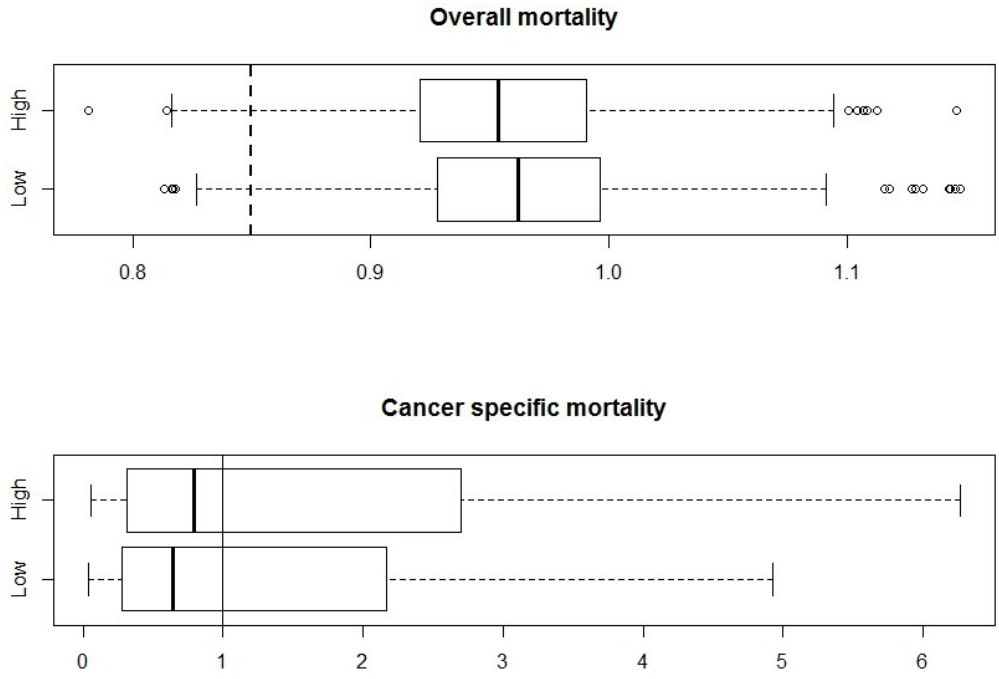

FIGURE 3: Hazard ratios for overall mortality and subdistribution hazard ratio for low grade and high grade patients (vertical dotted line corresponds to the hypothesed minimum for non-inferiority, normal line corresponds to the value 1 of subdistribution hazard ratio)

A competing risk regression model (64) was used to estimate sub distribution hazard ratios (SHR), in order to compare cancer specific mortalities. For low grade patients, the median SHR was 0.64 (IQR 0.28 – 2.16). For high grade patients, this value was 0.80 (IQR 0.32 – 2.70). The distributions of the different hazard and sub hazard ratios for the 1,000 simulated samples of low and high grade patients are presented in Figure 3.

3.6 SENSITIVITY ANALYSIS

A sensitivity analysis was performed for the low grade patient population. This was a one-way sensitivity analysis with respect to the other factors. The tested follow-up schedule consisted in quarterly visits for ten years and the program was run 500 times for 1,000 patients for each sensitivity analysis. Three factors were evaluated.

The first evaluated parameter was the effect of the treatment. This effect is considered as the risk of secondary metastasis after treatment of local recurrence compared with the risk of primary metastasis. If this parameter is equal to zero, a patient treated for LR will be free of risk of secondary metastasis. However, she is still at risk of primary metastasis and then death from cancer. For values of parameters equal to α, the risk of secondary metastasis after a treatment for cancer will be α times the risk of primary metastasis. For example, if $\alpha=2$, the patient's risk of secondary metastasis is twice her risk of primary metastasis and finally, her total risk of metastasis is three times her risk of metastasis before the LR. In this case, patients are considered completely adhering to the follow-up and the exams are considered 100% sensitive. The program was run for values of the α parameter between 0 and 9. The number of patients detected and treated does not vary according to the effect of the treatment, which is natural. However, Figure 4 shows that the number of deaths from cancer is increasing very slightly with α, with a constant variance. This increase is almost insignificant, justifying the assumption that patients with preclinical recurrence do not have a significant risk of secondary metastasis.

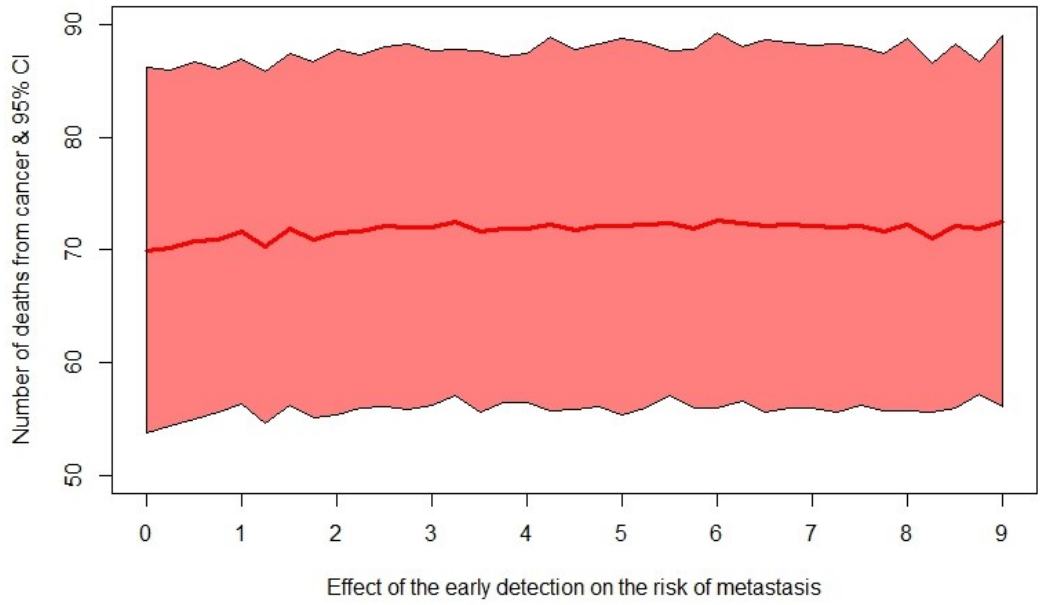

FIGURE 4: One way sensitivity analysis presenting the effect of the risk of secondary metastasis on death from cancer and the number of detected recurrences

The second parameter which has been evaluated is the sensitivity of the exam. In this case, it was considered that a patient treated after LR was free of risk of secondary metastasis. These patients were also considered to be perfectly adhering to the treatment. The number of patients detected in preclinical stage of LR naturally increases with the sensitivity of the examinations as shown in Figure 5. This implies a decrease of the number of deaths from cancer. One can notice that the variance of the number of deaths from cancer is stable for all the values of the sensitivity parameter.

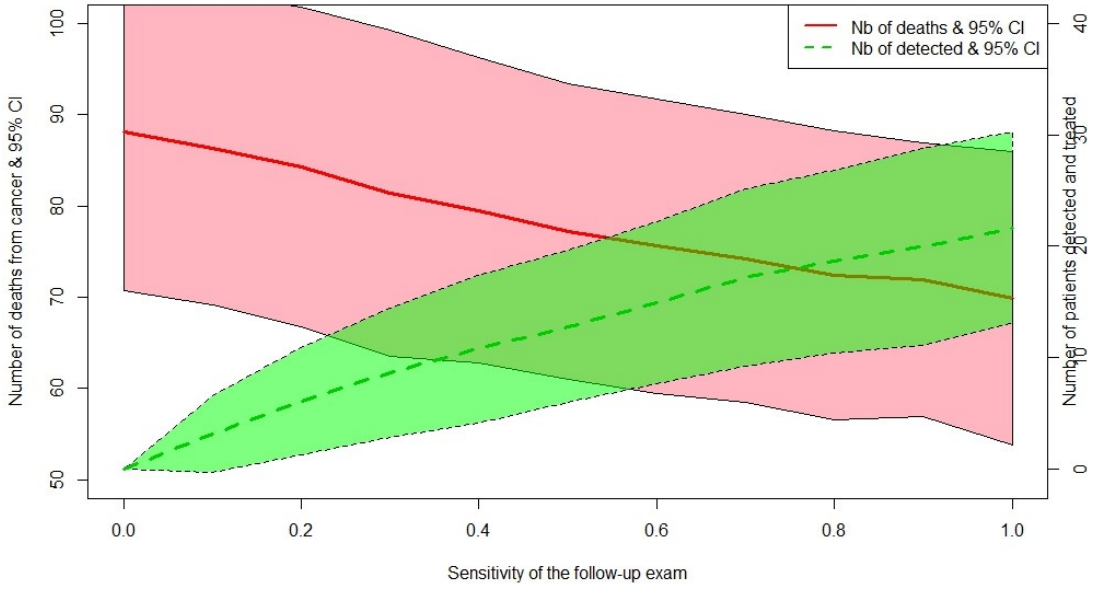

FIGURE 5: One way sensitivity analysis presenting the effect of the sensitivity of the exam on death from cancer and the number of detected local recurrences

Finally, a third analysis was run to evaluate the effect of the adherence to the schedule. The adherence to the follow-up schedule has been considered as randomly distributed. The parameter η corresponds to the probability for a patient to be present for a given follow-up visit. This value is considered constant for all visits and all patients. Figure 6 shows the same pattern as Figure 5. The effect of adherence to the follow-up schedule is identical to the one of sensitivity of the exam. A patient in LRP stage who misses a visit leads to the same consequence as if the patient had the examinations and if a false negative value was obtained.

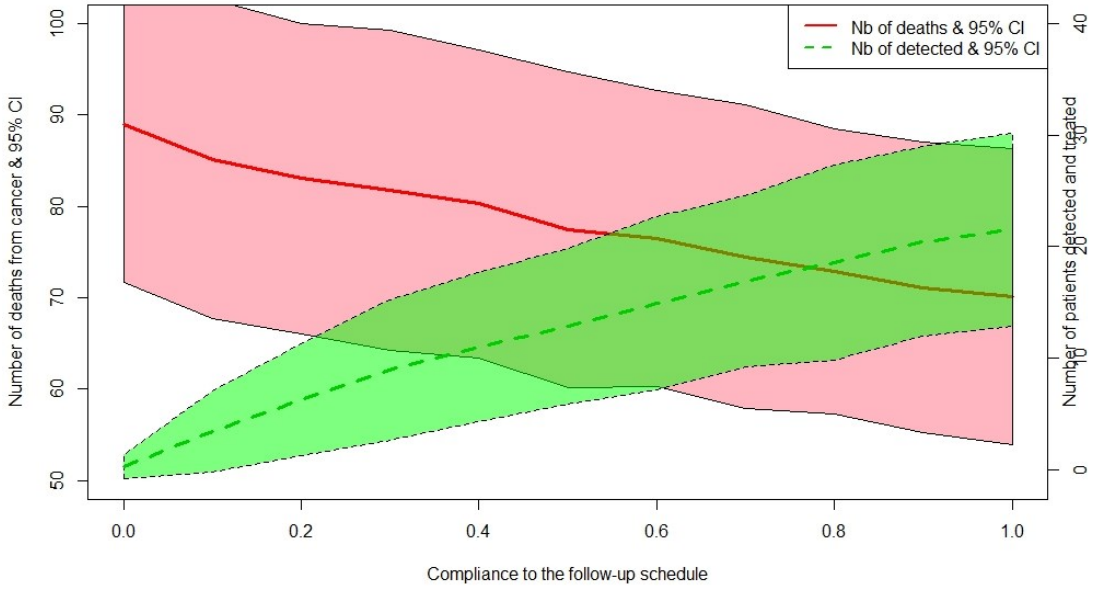

FIGURE 6: One way sensitivity analysis presenting the effect of the adherence to the follow-up schedule on death from cancer and the number of detected local recurrences

4 DISCUSSION

A new program of surveillance after primary treatment which permits time and costs savings without reducing patients' survival and quality of life will be preferred by both patients and health care personal. One can also decide to adopt a new program which improves survival or quality of life without being binding on either the patient or the health care provider. The proposed approach permits a realistic evaluation of the effect of a follow-up schedule with computer assistance. This method can be used as a first step before performing a randomized clinical trial that will be hard to undertake for such a problematic. The computer simulation program offers flexibility and can be adapted according to several aspects. It can handle patient's adherence. The program takes into account, for example, the fact that a patient could miss a scheduled visit, or come a few days after the appointment date. The computer simulated based trial also includes the sensitivity of the follow-up examinations. This also aims to fit to reality where neither individuals nor machines always perfectly abide the plans.

Simulation studies have been widely used to assess cost-effectiveness of health policies (65) and more generally as a tool of medical decision making (66). Rauner (67) has discussed the interest of computer simulation for the evaluation of intervention and treatment programs. She used a DES approach to evaluate strategies for prevention of mother-to-child transmission of HIV, based on data from Tanzania (68). This approach was also preferred by Davies et al. (69) to evaluate different policies for screening and controlling helicobacter pylori bacteria. The advantage of DES is its flexibility, its ability to handle variability, uncertainty and complexity (35).

Several authors have proposed different approaches to reduce or to reorganize follow-up. These can concern either the total length of follow-up (9,46) or the intervals between consecutive visits (6,11). Most of them have not been evaluated through a trial because of the eventual costs and the logistical burden of such actions. The computer based approach will permit to easily test these programs and possibly move to a further step.

The present application of the simulation method has shown the non-inferiority of no follow-up regimen compared to the lightest form of the NCCN recommended follow-up schedule. Jacobs et al. (21) have already shown that the European standard follow-up has a minimal impact on life expectancy of breast cancer patients. Finally, the problematic to know whether to follow up patients or not was highlighted. This question has been discussed in the case of cancer screening (19) and can be transposed to surveillance after primary treatment for cancer. Our method permits a first assessment about the usefulness, the efficacy of the non-inferiority of follow-up strategies before any application to patients which would lead to more efficacy and better ethics in research. The obtained results can be adjusted accordingly to the local realities such as patients' adherence to the study, sensitivity of the exams, etc.

Moreover, even if it does not improve survival, a follow-up schedule can provide sustainable utility. Life expectancy cannot be considered as the unique objective of surveillance of patients. Follow-up is valuable as psychological support for the patients. It can also be useful in providing public health information and advices and to observe the patients changes in habit. Additionally, the simulation

method will then find a large usefulness if a particular treatment strategy, presenting good cure prognosis for metastases is discovered and proposed for assessment. This approach can also be used to evaluate other outcomes such as QALY, YLL, cost effectiveness or economic sustainability.

The algorithm was built to be as flexible as possible. The goal is to be suitable for all cancer localizations and severities and also for all population types. Then almost no assumption is made for the time to event in this paper. The researchers will have to make their own assumptions, according to the specificity of their study. Times to events are generated following a mixture of a binomial and a Weibull model. The binomial part authorizes the possibility of cure. The Weibull distribution provides flexibility. The hypothesis of homogeneity is one particular case of this distribution. The other described functionalities (inclusion period, adherence to the schedule, sensitivity of the exam, etc.) are optional and should be included in the case where documented information is available. The proposed approach will then still be based on previous studies as the distribution parameters in the context of the follow-up strategy have to be known. The number of simulations required could not be defined to obtain a given accuracy with a theoretical value as proposed by Burton (15). It is therefore defined large enough to detect outliers and to focus the observations on the general cases. The sensitivity analysis has highlighted three important parameters to consider in such a trial. The effects of sensitivity of the exams and of the adherence of the patients seem obvious. However, we have not found documentation concerning the risk of secondary metastasis after a successful treatment of a recurrence. As patients are still at risk of metastasis after a successful treatment of primary cancer, the risk of secondary metastasis, even if the recurrence is considered as cured, should not be null. The analysis has shown that the effect of the follow-up program on overall survival could be sensitive to this aspect, but the relationship is rather weak.

A parameter which could be considered as missing in the proposed algorithm is specificity of the exams. We have considered that the follow-up visits could fail to detect a recurrence but the possibility of false positive tests was not considered. This does not have any impact on the main outcome which is survival as we consider that multiplicity of exams do not have any impact on the health status. This parameter will find its importance if the same approach is proposed for economic assessments such as cost-efficacy evaluations.

The proposed model does not handle multiple recurrences of the same type. A patient can experiment LR more than once in his lifetime. So the fact of being treated for the first LR does not exclude the risk of experiencing another such event type in the future. This aspect has not been taken into account for simplification reasons. Moreover, the transition between states can be modeled according to individual patient characteristics. Constant transition intensities have been used in the application for simplification purposes but the methodology can be applied to more complicated survival distributions with several parameters which handle cofactors. The risk factors of time to transition have been widely studied. De Bock et al. (58) have proposed for example hazard ratios for age, tumor size, node, chemotherapy and radiotherapy for transitions for local recurrence, primary and secondary metastasis, which can be used in a proportional hazards exponential model. Finally, patients may be at risk of several recurrence types, depending on the site (contralateral, second primary cancer …). A natural

history model should be more complete and be applicable to *K* different recurrences types. The follow-up examinations will have different efficacy parameters (sensitivity and specificity) and the effect of early detection should also be modeled accordingly to these *K* events. This can be considered in the extensions of the proposed algorithm.

The different programs can be obtained from the corresponding author upon request.

5 ACKNOWLEDGMENTS

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Chapitre V

Discussion et conclusion

Les travaux présentés ont permis de dégager des approches méthodologiques pour organiser des stratégies de surveillance individuelles en fonction des caractéristiques des patients traités du cancer. Ces stratégies sont définies en fonction des facteurs pronostiques des patients et des types de récidives auxquels ils sont à risque. Cette méthodologie se décrit en trois phases. La première étape consiste à déterminer la durée optimale pendant laquelle le patient devrait être soumis à cette surveillance [91]. La durée de surveillance est définie par rapport à la probabilité, pour un patient, de rechuter après la fin de son suivi, pondérée par les probabilités de succès d'un traitement de rattrapage en cas de détection précoce de cette rechute. Ces probabilités peuvent être estimées selon les caractéristiques aussi bien du patient que de la pathologie étudiée. La méthode d'estimation a nécessité l'utilisation de modèles de survie à risques compétitifs. L'approche directe de Jeong et Fine [72], consistant à modéliser les fonctions d'incidence cumulée des différents types d'événement, est celle qui s'adaptait à cette problématique. Les fonctions d'incidence cumulée, estimées au moyen de la distribution paramétrique de Gompertz, présentent une grande flexibilité et s'ajustent bien aux données empiriques. Un critère

de jugement simple à mettre en œuvre a ensuite été utilisé pour définir la durée de suivi optimale.

La principale limite à la méthode vient de la forme paramétrique des fonctions de risque. L'hypothèse de Gompertz [73] appliquée pour la définition des durées de surveillance a été démontrée comme très adaptée à la survie sans récidive. Par contre, elle présente une fonction de risque décroissante, donc monotone. Une plus grande flexibilité pourrait permettre de définir des cas marginaux qui pourront être observés. Jeong [92] présente une nouvelle fonction paramétrique permettant de modéliser des fonctions d'incidence cumulée plus flexibles. L'application de telles distributions (contenant quatre paramètres et présentant de nombreuses contraintes de supériorité ou de non-nullité) est cependant très peu parcimonieuse et ne permet pas des estimations précises. Finalement, la détermination de la durée de surveillance au moyen de la fonction de perte est une méthode novatrice en ce sens que peu de méthodes sont définies dans la littérature et que la question est toujours posée. De plus, elle s'avère plus complète que la méthode de Mould *et al.* [36], principalement par le fait qu'elle prend en compte plusieurs événements concurrents.

Lorsque la durée de suivi ainsi que le nombre de visites à programmer sont définis, la seconde phase de la méthode permet de dégager un calendrier optimal pour la surveillance de ce patient [93]. Ce calendrier consiste en la définition du rythme de suivi depuis la fin du traitement jusqu'à la date de fin de la surveillance. Il maximise la probabilité de détecter une récidive et de la traiter avec succès. En effet, la fonction d'utilité comprend les probabilités de détecter une récidive, selon qu'elle soit en phase précoce ou en phase tardive, pondérées par les pronostics de guérison associés. Ces probabilités peuvent également varier selon les caractéristiques individuelles du patient et les événements auxquels il est à risque. Le calendrier optimal est défini en modélisant l'histoire naturelle de la maladie lorsque le patient est dans la phase post-thérapeutique. Cette histoire naturelle distingue les différents types de récidives. Pour chaque type de récidive, l'effet du traitement est considéré si la détection est effectuée en phase précoce ou si le diagnostic n'est réalisé qu'en phase clinique. Il en résulte une approche méthodologique adaptée aux situations réelles ainsi qu'aux capacités technologiques dans la prise en charge des récidives.

La modélisation de l'histoire naturelle, pour la programmation optimale des visites de suivi, fait cependant l'hypothèse forte d'un processus de Markov homogène. Cette hypothèse implique que le risque instantané de récidive est constant avec le temps. La même supposition est émise pour le risque instantané de passage en phase clinique pour les patients se trouvant dans une phase précoce de leur récidive. De plus, le modèle suppose que le temps passé dans la phase pré-clinique est indépendant de la date d'entrée dans cette phase. Ces hypothèses sont assez fortes. Dans le cas du cancer du sein, par exemple, il a été démontré que la distribution des risques de récidive n'est pas homogène [94, 95]. Un premier pic de récidives est observé deux ans après le traitement. Certains auteurs [96] parlent également d'un second pic à cinq ans. Finalement, des approches non homogènes [79, 97] sont de plus en plus proposées. Cependant, l'hypothèse de Markov homogène se révèle être la meilleure option en cas de faible connaissance de la distribution exacte des récidives.

Enfin, il est toujours très difficile de faire la preuve de l'efficacité d'une stratégie de surveillance. Cet exercice demande des techniques d'évaluation cliniques très codifiées dans la pratique et très difficiles à appliquer dans le cadre de la surveillance post-thérapeutique. La méthode de référence pour cette évaluation est l'essai randomisé, et dans le cas des stratégies de suivi, un essai clinique de non-infériorité. Cependant, pour des raisons d'éthique, il est nécessaire d'effectuer des simulations afin de s'assurer que la mise en œuvre d'un tel essai n'entraîne pas de conséquences sur la qualité de la prise en charge des patients. La méthode présentée propose un algorithme qui permet de reproduire un essai clinique par simulation numérique. Cette étape apportera les garanties nécessaires avant l'intervention sur des patients. L'algorithme proposé est basé sur la simulation de l'histoire naturelle des patients depuis la fin du traitement primaire jusqu'à leur décès.

Une approche par simulation dynamique, basée sur la technique de simulation des événements discrets, a été utilisée afin d'assurer le maximum de flexibilité et d'adaptabilité. Les patients transitent par différents états à des dates qui sont définies en fonction de leurs caractéristiques individuelles, de la distribution des événements auxquels ils sont à risque, des différentes probabilités de guérison, etc. L'approche par simulation des événements discrets est efficace pour caractériser les transitions des patients entre différents

états. Cette approche nécessite cependant la prise en compte de plusieurs hypothèses pour définir les éléments de l'histoire naturelle adaptée à la localisation du cancer et aux caractéristiques individuelles du patient. La principale force de l'approche par simulation de l'histoire naturelle de la maladie depuis la fin du traitement est pourtant sa capacité d'adaptation au type de cancer, au type de patients ainsi qu'aux capacités de l'établissement de prise en charge.

Le fait de distinguer systématiquement les types de récidives permet de prendre en compte l'efficacité de la surveillance. En effet, un suivi post-thérapeutique ne trouvera son intérêt que s'il est avéré qu'un patient dont on détecte tôt la rechute aura une espérance de vie et une qualité de vie améliorée de façon considérable. Cependant la capacité à améliorer l'espérance de vie est sans cesse évolutive au vu de la recherche active pour de meilleures techniques et technologies de prise en charge. De plus, les connaissances et les capacités de guérison diffèrent selon le type de récidive. Ainsi, un modèle qui permet de prendre en compte, de façon indépendante, la capacité à guérir les différents types de récidive se retrouve bien adapté au contexte de la lutte contre le cancer.

La modélisation de la surveillance post-thérapeutique du cancer trouve aussi son utilité dans le fait qu'elle permettra de comprendre et de contrôler certains facteurs. La connaissance des coûts globaux du suivi permet de mieux planifier les budgets aussi bien pour l'assurance maladie qu'au niveau des établissements de soins et des patients. Il en va aussi de l'organisation logistique et matérielle des services concernés étant donné que ceux-ci peuvent avoir une idée de la charge de travail à prévoir, des examens de radiographie ou d'imagerie à venir, etc. La connaissance de cette charge de travail permet aussi d'organiser le flux des visites et par suite, l'organisation interne du service. La simulation numérique a permis, pour une cohorte donnée, d'estimer le nombre total d'examens à programmer par rang de visite. Un calendrier estimatif peut être mis en place par l'établissement qui permettra la planification de ses activités de suivi sur une période. Ceci lui permettra d'anticiper les difficultés potentielles. La présence de ce calendrier pourra par ailleurs permettre de modifier les rythmes de suivi par rapport aux ressources financières et logistiques disponibles ou par rapport à la capacité de l'établissement à fournir un service de qualité.

Plusieurs conditions sont posées pour les futures directions à donner à la surveillance post-thérapeutique du cancer. Tout d'abord, Kraeima *et al.* [98] relèvent la nécessité de l'adapter aux risques individuels. Francken *et al.* [41] relevaient ainsi le manque d'efficacité des programmes courants de surveillance qu'ils attribuaient essentiellement au fait que ceux-ci étaient plutôt généralistes et non individualisés. Les approches de détermination d'une telle surveillance sont cependant toujours empiriques. Cela est dû à l'insuffisance de données et de modèles traitant de cette question. C'est dans ce sens que Robertson *et al.* [99] soulignent l'utilité de banques de données, notamment de registres nationaux, afin d'identifier ou de concevoir des stratégies réalisables. Ces éléments permettront finalement d'évaluer l'utilité [100] de celles-ci et de les confronter à leurs effets nocifs [101]. Plusieurs stratégies sont proposées dans la littérature comme alternatives au suivi tel qu'effectué couramment.

Par ailleurs, alors que les questions sur l'opportunité d'un suivi ont longtemps été discutées, plusieurs auteurs s'accordent à étendre ses objectifs. Les critères de jugement de l'efficacité de la surveillance ne devraient en effet plus se réduire au cadre clinique. Hewitt *et al.* [4], dans leur étude, ont reporté que généralement les patients étaient satisfaits de l'aspect clinique de la surveillance mais trouvaient encore à redire quant à l'atteinte de leurs besoins psychologiques. Le suivi après le traitement, tel que voulu par les patients, devrait être un outil d'accompagnement psychologique pour leur réinsertion dans la société.

Au vu de l'augmentation du nombre de patients en surveillance post-thérapeutique, le problème de la capacité des instituts spécialisés de prise en charge des malades du cancer à procurer des services de qualité à tous les patients est crucial. De plus, l'oncologue est souvent sollicité, pendant ses visites, pour des problèmes de santé non liés au cancer. Cet état de fait pose des difficultés étant donné que celui-ci a besoin de se concentrer sur les problèmes spécifiques au cancer sans s'attarder sur les autres services de santé primaire. Plusieurs sociétés ont donc proposé que le médecin généraliste assure le suivi post-thérapeutique, notamment pour ce qui concerne le cancer du sein [7] ou le cancer colorectal [12]. L'opportunité de cette option a ensuite été confirmée par différents essais cliniques [102, 103].

D'autres auteurs vont plus loin en discutant de la possibilité d'un suivi post-thérapeutique

effectué par des infirmiers spécialisés. En effet, Strand *et al.* [104] ont évalué l'opportunité du suivi par les infirmiers en termes de satisfaction du patient, d'utilisation des ressources et de sécurité pour des patients opérés pour un cancer rectal. Finalement, les services du chirurgien ne se sont révélés nécessaires que dans peu de cas alors que les coûts financiers étaient équivalents. Une expérience similaire menée par Leahy *et al.* [105] sur des patients traités d'un cancer de la prostate a montré que le suivi par les infirmiers était très satisfaisant.

L'étude de Leahy *et al.* [105] a également permis l'introduction d'un autre élément dans la surveillance qui est la technologie. Le suivi était en effet effectué principalement au téléphone. Dans leur revue systématique, Dickinson *et al.* [106] discutent de l'utilité des technologies pour la surveillance. Celles-ci permettraient un niveau de sécurité acceptable aux patients quoique des investigations supplémentaires soient requises. Enfin, Forsythe *et al.* [107] ont relevé une des principales insuffisances des programmes de surveillance. Les calendriers, les technologies et les acteurs mis à contribution n'apportent toujours pas un élément essentiel dans celui-ci, à savoir l'accompagnement psycho-social.

Les résultats théoriques produits dans la présente thèse peuvent être appliqués à toutes les localisations des cancers. Ils peuvent plus généralement s'appliquer à toutes les maladies chroniques où un suivi des patients améliore leur état. En perspective, les méthodes et techniques développées dans le présent document seront utilisées et appliquées à des problématiques diverses.

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TITRE : Individualisation du suivi post-thérapeutique des patients traités du cancer en fonction des facteurs pronostiques et du type de rechute
DIRECTEURS DE THÈSE : Pr Christine THOMAS-AGNAN, Dr Thomas FILLERON
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RÉSUMÉ : Les questions de l'organisation de la surveillance des patients ayant reçu un traitement pour un cancer sont toujours ouvertes. Les pratiques courantes sont principalement fondées sur des recommandations d'experts. Peu de preuves scientifiques sont posées pour les valider. Cette thèse propose une méthodologie pour organiser une surveillance post-thérapeutique des patients traités du cancer. Cette surveillance sera individualisée en tenant compte des caractéristiques du patient. Elle sera aussi flexible en s'adaptant aux caractéristiques propres de la maladie, de sa sévérité et des différents types de récidives attendues. Une première partie permet de déterminer la durée optimale de suivi du patient. Les fonctions d'incidences cumulées des différents types de récidives sont modélisées par une approche directe de modélisation de risques compétitifs. La deuxième propose une méthodologie pour fixer les dates de visite de façon optimale. Cette méthode passe par la modélisation des dates d'apparition des événements par une approche multi-états en utilisant une hypothèse de Markov homogène. Enfin, un algorithme est proposé pour évaluer un programme de surveillance post-thérapeutique. Cet algorithme permet de simuler de façon numérique les transitions dynamiques par une technique de simulation des événements discrets. L'ensemble des modèles se basent sur l'histoire naturelle de la maladie.
Mots clés : *Cancer* ; *Surveillance post-thérapeutique* ; *Planification optimale* ; *Modèle de l'histoire naturelle* ; *Modèles multi-états* ; *Modèles de Markov* ; *Risques compétitifs.*

ABSTRACT : There still are open questions about the organization of the surveillance of patients who received treatment for cancer. Current practices are mainly based on expert recommendations. Little scientific evidence are found to confirm them. This thesis proposes a methodology to organize the post-therapeutic follow-up of patients treated for cancer. This follow-up will be individualized according to the patient's characteristics. It will also be flexible and adapt to the characteristics of the disease, its severity and the expected types of recurrences. The first part considers the determination of the patient's follow-up period. The cumulative incidence functions of the different recurrence types are modeled by a direct competing risks modeling approach. The second part proposes a methodology to determine the optimal visit dates. This approach involves modeling the dates of recurrence by a multi-state approach using a homogeneous Markov assumption. Finally, an algorithm is proposed to evaluate a post-therapeutic surveillance program. This algorithm simulates dynamic states transitions by a discrete events simulation approach. All models are based on the natural history of the disease.
Keywords : *Cancer* ; *Post-therapeutic surveillance* ; *Optimal schedule* ; *disease history model* ; *Multistate model* ; *Markov models* ; *Competing risks.*

DISCIPLINE ADMINISTRATIVE : Mathématiques appliquées et application des mathématiques