Early stage cervical cancer : quality of cancer care and quality of life

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Chapter 4

An individual prediction of the future (disease free) survival of patients with a history of early stage cervical cancer; multi-state model.

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Abstract

Objective: To evaluate the possibility to give a prediction of the future (disease free) survival, given the fact that a patient with a history of early stage cervical cancer has been disease free for a specific period after treatment.

Methods: Between January 1984 and April 2005, 615 patients with cervical cancer stage I-IIa underwent radical hysterectomy with or without adjuvant radiotherapy. The Kaplan-Meier method was used to detect statistical significance and multi-state risk models to estimate the influence of covariates and to generate predicted survival curves by simulation. Simulations were done for patients with positive lymph nodes (n=123), patients with negative lymph nodes (n=492) and four hypothetical patients.

Results: The 5-year cancer specific survival and disease free survival of the entire group was 84% and 76%, respectively. The probability of death of the two lymph node groups and the four hypothetical patients were demonstrated in predicted cumulative probability plots.

Conclusions: It is possible with multi-state risk models to give a detailed prediction of the future (disease free) survival, given the fact that a patient has been disease free for a specific period after treatment. This possibility is an important step forward to improve the quality of cancer care.

Introduction

The prognosis of early stage cervical carcinoma after radical hysterectomy is excellent in most cases, with 5-year survival rates of 80-90% (1-4). However, recurrences confront the physician and the patient with a rather dismal prognosis, leading to the death in more than 85% of cases (5;6) and this 'sword of Damocles' is often present in the patient's mind. When a patient confronts the physician with questions about the exact risk of recurrence or death in their individual case by time, it can be difficult and sometimes even impossible to answer this adequately. An adequate answer could also provide information to individualise the treatment management and the (length of) programs of surveillance. Furthermore, it could provide psychological support.

Standard survival data measure the time span from some time origin until the occurrence of one type of event. If several types of events (like recurrence or death) occur, a model describing progression to each of these competing risks is needed. For a cervical cancer patient, if the event of interest is death, then recurrence becomes an intermediate event worth modelling. These intermediate event types provide more detailed information on the disease/recovery process and allow for more precision in predicting the prognosis of patients.

Multi-state models may be considered as a generalization of the basic framework for dealing with survival data to the case where several (possibly competing) events occur successively over time. The occurrence of successive events constitutes the transitions from an initial state to a final state. Here, the states of these cervical cancer patients are recurrence and death. Furthermore, these models allow the incorporation of prognostic factors in order to study the influence of these factors on each of the transition rates. Multi-state models can be used to predict the likelihood to reach a specific future state (e.g. recurrence) on the basis of their present state at various time intervals following initial treatment.

The aim of this study is to give a prediction of the future (disease free) survival, given the fact that a patient has been disease free for a specific period after treatment. For this means a database was used in which all clinical and pathological parameters of patients with cervical cancer treated in our institute were prospectively collected since January 1984. Statistical analysis was done with multi-state risk models specifically designed for this purpose.

Patients and Methods

Study group

Between January 1984 and April 2005, 643 patients with stage I-IIa cervical carcinoma were treated at the department of gynaecology of the Leiden University Medical Centre (LUMC) with a radical hysterectomy and pelvic lymphadenectomy (RHL) with or without adjuvant radiotherapy. All patients in the

study were treated by the same four gynaecologic oncologists. Clinical and pathological parameters were prospectively collected in a database. Two patients were excluded from this analysis because they received both pre- and postoperative radiotherapy, nine because of preoperative chemotherapy and 17 because they received postoperative chemotherapy. Of the remaining 615 patients, 536 (87%) underwent a radical hysterectomy according to Rutledge type III (7) and pelvic lymphadenectomy, and 79 (13%) patients a class II (Te Linde) extended hysterectomy, all in combination with pelvic lymphadenectomy.

Staging and pathology

Preoperative staging was performed according to the guidelines of the International Federation of Gynaecology and Obstetrics (FIGO) (8). The following characteristics from the pathology slides were documented: tumour size, histologic tumour type, depth of invasion, parametrial involvement and capillary lymphatic space status (CLS). When no tumour was found in the material from the radical hysterectomy specimen, presurgical data from conisation or biopsies were used. The depth of invasion was measured from the most superficial epithelial-stromal interface of the adjacent intra-epithelial process to the lower limits of invasion (9). CLS was regarded positive when neoplastic cells were seen within endothelium lined spaces.

Radiotherapy

The indications for postoperative radiotherapy were (1) node positivity, (2) parametrial infiltration, (3) positive or non radically free (less than 5 mm) surgical margins, (4) the combination of at least 2 of the following 3 risk factors: pathological tumour size (≥40mm), depth of invasion (≥ 15 mm) and CLS involvement. Seven patients had individual reasons for postoperative radiation, such as surgical or medical difficulties to complete the operation as planned or tumour spill during surgery. External beam radiotherapy was administered to the pelvis using a four-field box technique. Patients were treated with 10 MV photons from a linear accelerator to a total dose of 46 Gy in 2 Gy fractions, specified at the isocentre. A brachytherapy boost was given to the vaginal vault in case of extensive CLS (68% of the patients), using vaginal colpostats, 15 Gy low dose rate or equivalent dose, prescribed at 5 mm from the vaginal mucosa.

Data analysis

The follow-up was closed on April 2005 and ranged from 0 to 223 months with a mean duration of 53 months. The disease free survival (DFS) was defined as the time from RHL to cytologically or histologically proven evidence of recurrent disease or date last seen. Cancer specific survival (CSS) was defined as the time from date of operation to death by tumour or date last seen. Survival after recurrence was defined as the time from cytologically or histologically proven evidence of recurrent disease to death by tumour or date last seen. Survival curves were made using the Kaplan-Meier method (10). The dif-

ference in DFS and CSS by treatment regimen was evaluated using the log-rank test (10;11). A p-value <0.05 was considered statistically significant. The variables that have been taken into consideration in the analysis of individual patient survival are; lymph nodes involvement, tumour size, depth of invasion, CLS, parametrial invasion, adenosquamous carcinoma and positive surgical margins.

Multi-state modeling

After therapy, only a fraction of patients encounters a relapse. After relapse, the probability of dying (within five years) is high. So we are dealing with a survival process with three states: the initial state directly after therapy, the relapse state and death. Every patient starts in the initial state and may undergo a transition to the second state (relapse) or (from the second state) to the third state (death). The proper way to model such a process, on the basis of observed data, is multi-state survival analysis. The dependence of the hazard of each possible transition as a function of time and covariates (like for example lymph node status and tumour size) is modelled by the proportional hazard approach, commonly known as the Cox model.

The first phase of multi-state modelling is the estimation of coefficient values for the covariates and the baseline hazard curves. In a second stage these results are used to predict individual survival curves, given the values of the covariates for a (virtual or real) patient.

The occurrence of relapse strongly increases the probability of a fatal outcome. Conversely, the longer a patient stays relapse-free, the better her chances for survival. The methodology allows the computation of conditional survival curves, given the length of the relapse-free period. Such curves allow doctors and patients to get a better estimate of future prospects.

The multi-state analysis was performed with a library of statistical functions for the R system, an open-source statistical system (12). The library was developed at the Department of Medical Statistics and Bioinformatics of the LUMC (13). It uses established routines for estimation of the proportional hazards sub-models. To construct compound survival curves (in the present case for the path from disease-free to recurrence to death), a simulation approach is used, generating event histories for a large number of pseudo-patients with given values of their covariates (14).

The multi-state model makes the usual assumptions of the Cox model: the effect of covariates can be modelled as a change in hazards of events (recurrence or death) which is constant over time. Another important assumption that we make is that of "clock reset": at the moment of relapse, time starts running in this state, independent of the length of the spell in the disease-free state. Thus, the clock is reset every time the patient enters a new state.

The predicted (conditional) survival functions are based on the non-parametric estimate of baseline hazard that results from the Cox model. This means that the simulation uses the observed time points in the data, because the Cox model by construction "knows nothing" about intervals between events. As a result a simulated survival curve looks like a staircase with unequal steps. We apply P-splines to produce smooth curves which allow easy interpolation (15).

Characteristics	Patients (n=615)	
	n	%
Age		
≤30	47	8
31-60	479	78
61-90	89	15
FIGO		
Ia	21	3
Ib	510	83
IIa	84	14
Cell type		
Squamous cell	443	72
Adenocarcinoma	125	20
Adenosquamous	34	6
Double tumor	4	1
Others	9	2
Lymphnode metastases		
Yes	123	20
No	488	79
Not done	4	1
Parametrial infiltration		
Yes	58	9
No	541	88
Unknown	16	3
Non-radical surgical margins		
Yes	94	15
No	505	82
Unknown	16	3
Tumour size		
≥ 40mm	167	27
<40mm	345	56
Unknown	103	17
CLS*		
Positive	218	35
Negative	349	57
Unknown	48	8
Depth of invasion		
≥15mm	189	31
<15mm	405	66
Unknown	21	3
Adjuvant radiotherapy		
Yes	254	41
No	361	59

Table 1. The clinical and histological characteristics of the 615 patients.

* Capillary lymphatic space involvement.

Results

The age of the patients ranged from 21 to 88 years, with a mean of 45. Forty one percent received adjuvant radiotherapy. The clinical and histological characteristics of the patients are listed in Table 1. Of the 615 patients in the study population, 116 (19%) developed recurrence of disease and 80 (13%) died of the disease. The interval from RHL to recurrence ranged from 2-134 months, with a median of 26. The interval from recurrence to death ranged from 1-47 months with a median of 15. Sixty-three percent of the recurrences occurred in the first 2 years after the therapy. Only 8 % of the relapses occurred after 5 years. The 5-year CSS (Fig. 1) and DFS of the entire group was 84% and 76%, respectively.

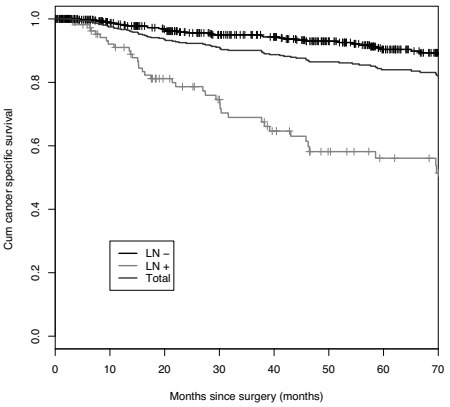

Figure 1. Cancer specific survival of the entire group (n=615), the patients with positive lymph nodes (n=123) and the patients with negative lymph nodes (n=492). Legend: Total, entire group; LN+, positive lymph nodes; LN-, negative lymph nodes. See colour figure page 151.

The 5-year CSS (Fig.1) and DFS were 56% and 43% respectively, among the patients with positive lymph nodes (n=123) in contrast to the patients with negative lymph nodes (n=492), who had a 5-year CSS (Fig.1) and DFS of 90% and 84%, respectively. The differences in CSS and DFS between the 2 groups were statistically significant (p<0.001 and p<0.001, respectively). Table 2 shows the risk factors and their estimator of coefficient in the two stages.

Risk factors	**Disease free-recurrence**		**Recurrence-death**	
	Coefficient	**SE**	**Coefficient**	**SE**
Lymph node involvement	0.737	0.270	0.891	0.345
Tumour size	0.032	0.007	0.013	0.010
Depth of invasion	-0.003	0.017	0.000	0.025
CLS*	0.648	0.278	-0.828	0.389
Parametrial invasion	0.761	0.281	-0.486	0.427
Adenosquamous carcinoma	0.907	0.353	0.011	0.454
Non-radical surgical margins	0.391	0.286	0.851	0.383

Table 2. Risk factors and their estimator of coefficient and Standard error (SE) in the two stages, disease free to recurrence and recurrence to death. * Capillary lymphatic space involvement.

The predicted probability of death of patients with and without positive lymph nodes is shown in Figure 2. If a patient with negative nodes survives 60 months since therapy without recurrence (T60), she will have a probability of only 1.4% (0.014) that she will be death after another 100 months (160 months since therapy). On the other hand, if a patient with positive lymph nodes has no recurrence at 60 months since therapy (T60), she will have a probability of 73.3% (probability of death 0.267) that she is still alive after another 100 months.

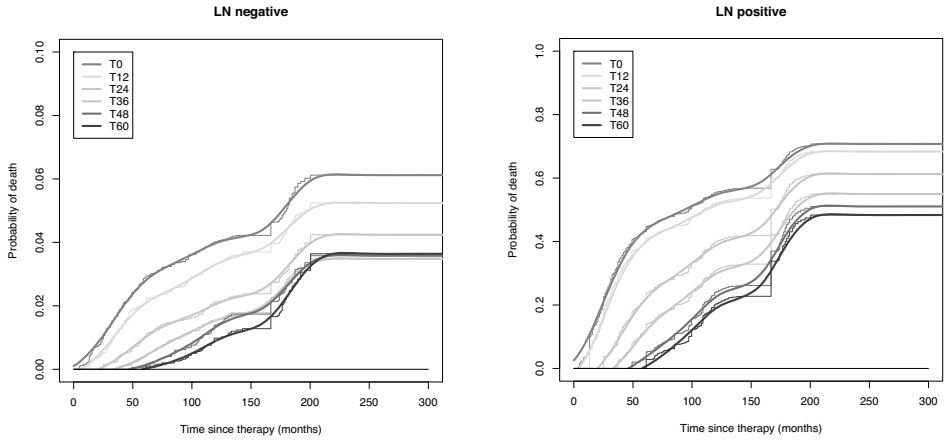

Figure 2. Predicted cumulative probability plots of patients with early stage cervical cancer with negative lymph nodes (LN negative) and with positive lymph nodes (LN positive).
Legend: T0=0 months, T12= 12 months, T24=24 months, T36=36 months, T48=48 months and T60=60 months. See colour figure page 151.

To demonstrate the results of an individual prediction of the future survival we defined four hypothetical patients (A, B, C and D) for simulation. The different risk factors that were used for simulation in these four hypothetical patients are shown in Table 3. Figure 3 shows the predicted cumulative probability plots

Risk factors	**Patient A**	**Patient B**	**Patient C**	**Patient D**
Lymph node involvement	+	-	-	+
Tumour size	45 mm	18 mm	50 mm	30 mm
Depth of invasion	18 mm	7 mm	20 mm	10 mm
CLS*	+	-	+	-
Parametrial invasion	+	-	-	-
Adenosquamous carcinoma	+	-	-	-
Non-radical surgical margins	+	-	-	-

Table 3. The values of the different risk factors of four hypothetical patients used for simulation. * Capillary lymphatic space involvement.

of patient A, B, C and D. When patient C survives 12 months without recurrence (T12) she has a probability of 21.5 % to be death after 60 months since surgery. But when there is still no sign of the disease after 24 months (T24) the probability that she will be death after 60 months since surgery will be reduced to 12.7 % (Fig.3). When patient A, B, C and D all experience no recurrence after 12 months, the probability to death after 24 months since treatment is 95.9%, 1.9%, 9.2% and 25.1%, respectively (Fig.3).

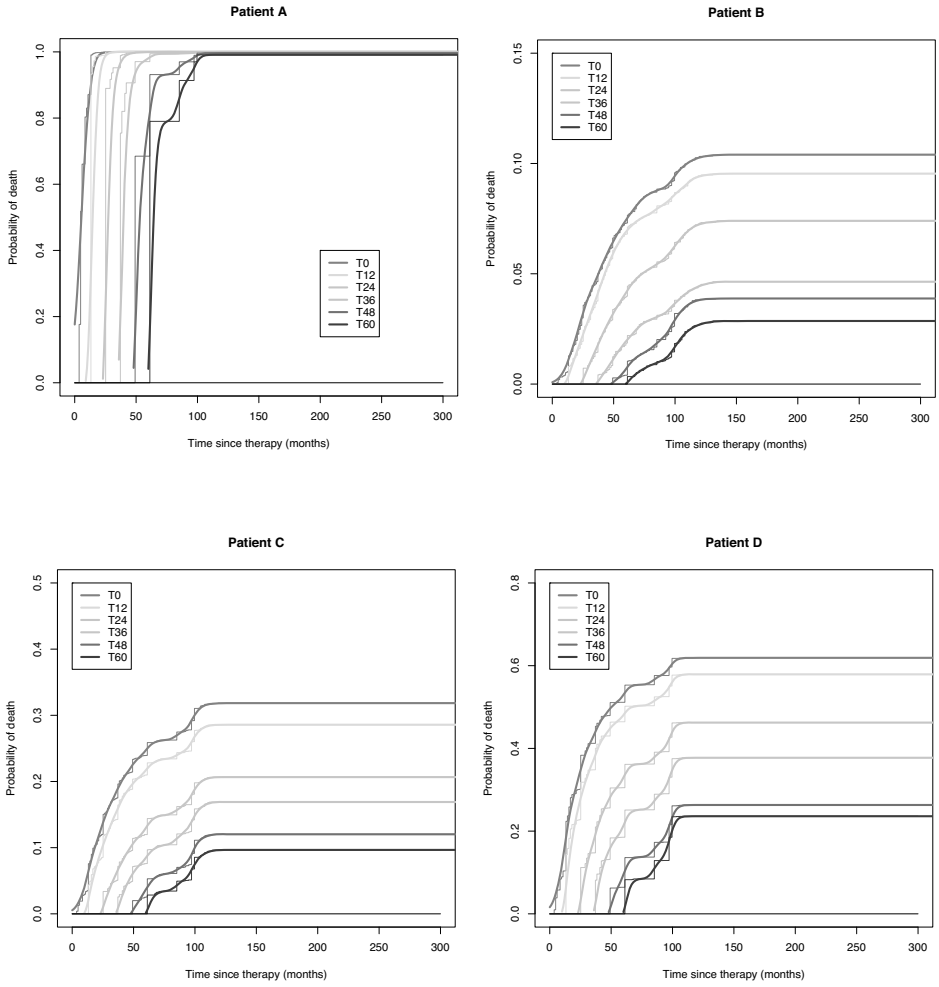

Figure 3. Predicted cumulative probability plots of patient A, B, C and D (Table 3). Legend: To=0 months, T12= 12 months, T24=24 months, T36=36 months, T48=48 months and T60=60 months. See colour figure page 152.

Discussion

The possibility to give a detailed prediction of the future (disease free) survival was evaluated, given the fact that a patient has been disease free for a specific period after treatment. The characteristics of our patients in terms of CSS, DFS and the time of recurrence are in accordance with the literature (1-6;16-20), defining our study group as a standard population of patients with early stage cervical cancer. Finally, the current study indicated that with the use of multi-state risk models a prediction of the future (disease free) survival could be calculated.

The strength of the current study is the fact that a prospective database and a consecutive series of patients were used. Besides, all patients were treated by the same group of gynaecologic oncologists. Furthermore, multi-state risk models were used. In complex survival data such as data of patients after a RHL for the treatment of early stage cervical cancer, a number of important (time-) dependent variables (positive lymph nodes, metastases, recurrence) must be taken into consideration in the analysis of patient survival. Multi-state modelling is proposed, analyzing each state separately using e.g. Cox regression models. This enabled us to evaluate which risk factors influence the prognosis of a patient and the complete model could hereafter be used to synthesize patient survival. On the other hand, uncertainties can occur at several levels. Given the model output, there is simulation uncertainty, which can be reduced by simulating enough pseudo-patients. Because the model is based on limited data (615 patients), there are uncertainties in the parameter estimates; no amount of simulation can reduce these. Next, there is a third source of uncertainty. While the moment of death is known with great precision, the relapse state of a patient is often determined at follow-up visits. So the exact date of transition—if such a concept is meaningful at all—cannot be known. In survival analysis parlance this is known as interval censoring. Commonly the date of the follow-up visit at which relapse is ascertained is taken as the moment of its occurrence. We have followed that convention too. Finally, since multi-state survival analysis is a recently developed analysis method it is yet not easy to provide confidence intervals for the probabilities. This will be a future development.

Various types of multi-state models have previously analysed other types of treatment and disorders, including bone marrow transplantations (21), liver transplantations (22), diabetes (23), quality of life in cancer (24), malaria (25) and nosocomial infections in intensive care unit patients (26). The current study is the first study that used multi-state risk models to evaluate the future (disease free) survival of patients treated for cervical cancer stage I-IIa.

Almost all studies evaluating the follow-up, use a minimum follow-up period of 5 years (1-4). However, the majority (70-90%) of recurrences are diagnosed within the first 2 years of initial treatment (5;6;18-20). Besides, there seems to be no consensus in policy as post treatment surveillance programs differ widely among institutions (27) and numerous reports in the literature have shown that routine clinical follow-up surveillance is ineffective in detecting recurrent disease or in achieving a more favourable outcome (20;28-31). When a prediction of the future (disease free) survival could be calculated for

an individual patient, it could provide information to individualise the treatment management and the (length of) programs of surveillance and this obviously will benefit cost and time implications. Furthermore, improving the quality of cancer care will undoubtedly lead to a better quality of life for cancer patients.

As the experience with this new statistical approach will increase, it can only be a matter of time before gynaecologic oncologists will have a program, based on multi-state modelling, on their computer. By this program they will be able to fill in all the individual adverse risk factors, which will lead to the prediction of the future (disease free) survival for that individual patient.

Until the results of other trials are known, the outcome of the present study shows the possibility to give a prediction of the future (disease free) survival, given the fact that a patient has been disease free for a specific period after treatment. It can be concluded that this possibility is an important step forward to improve the quality of cancer care.

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