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ORIGINAL ARTICLE – GASTROINTESTINAL ONCOLOGY

A Simple Tumor Load-Based Nomogram for Surgery in Patients with Colorectal Liver and Peritoneal Metastases

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ABSTRACT

Background. The decision to perform optimal surgery when peritoneal metastases (PM) are associated with liver metastases (LM) is extremely complex. No guidelines exist. The purpose of this study was to present a simple and useful statistical tool that generates a graphical calculator (nomogram) to help the clinician rapidly estimate individualized patient-specific survival before undergoing optimal surgery.

Materials and Methods. An analysis of 287 patients with liver metastasis (LM), 119 patients with peritoneal metastasis (PM), and 37 patients with LM + PM, who underwent optimal surgery plus chemotherapy between 1995 and 2010 was performed. A minimal number of parameters were taken into account to obtain a nomogram that would be very simple to use. With the overall tumor load as the main prognostic factor, we included the number of lesions for LM and the peritoneal carcinomatosis score (PCI) for PM. The Cox model was used to generate the nomogram.

Results. The 5-year overall survival was, respectively, 38.5, 36.5, and 26.4 % in the LM group, the PM group, and the LM + PM group. The summation of 3 parameters (the number of LM, the PCI, and the type of surgery [liver resection, HIPEC, or both]), makes it easy to calculate a score that graphically corresponds to an estimation of survival after optimal surgery (nomogram). It can be used for LM alone, PM alone, or both.

Conclusions. A graphic nomogram that is simple to calculate and easy to use enables us to rapidly appreciate the prognosis of patients according to the number of LM, the PCI, or both. This nomogram must be validated in prospective studies in other tertiary centers.

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Indications for surgery for liver metastases (LM) have recently been modified.[1] Likewise, indications for surgery for peritoneal metastases (PM) have also advanced considerably over the last 10 years.[2–4] Different scoring systems and nomograms have been published for both to help determine the prognosis.[2,4–8]

The presence of extrahepatic lesions, if resectable, is no longer a contraindication to hepatectomy.[9–12] Similarly, the presence of LM is not a contraindication to treating PM with a curative intent.[2,13] Moreover, recent data have shown that overall survival (OS) of patients surgically treated for LM is very close to that of patients surgically treated for PM and that the subgroup presenting limited PM could enjoy better OS than patients treated for LM.[14–17]

Finally, there are no guidelines and no large series in the literature that show clinicians what to do when faced with a patient simultaneously exhibiting LM and PM, both of which are eventually resectable. Combining existing predictive scores respectively for LM and for PM is very complex and most of the time impossible. Furthermore, most of these scores are hard to use in daily practice, unlike a nomogram. None of the existing scores concern LM associated with PM.

A nomogram is a statistical tool that generates a simple graphical representation of a complex statistical model. It helps the clinician to graphically determine individualized, patient-specific survival rapidly without doing any complex calculations.

The objective of this article is to present a risk prediction model for 5-year OS of patients presenting with LM, or PM, or both by taking in account the wide variability in survival due to the number of LM and the extent of PM. This risk model will then be used to develop a user-friendly clinical assessment tool (a nomogram) that will enable physicians to rapidly estimate survival based on easily acquired input values.

PATIENTS AND METHODS

Patient Selection

From January 1995 to December 2010 any patients undergoing a liver resection (LR), complete cytoreductive surgery followed by hyperthermic intraperitoneal chemotherapy (CCRS–HIPEC), or both of these procedures (LR + CCRS–HIPEC) for stage IV colorectal cancer were included in a prospective database.

In our tertiary cancer center, a multidisciplinary team comprising surgeons, oncologists, radiologists, and pathologists chose the best therapy for each patient, after a complete preoperative workup. Patients exhibiting disease progression under chemotherapy were excluded. The goal was to achieve optimal surgery. For patients presenting synchronous LM and PM, combined procedures were proposed to patients with a limited number of metastases and a limited PCI score deemed fit enough to undergo this aggressive surgery. The general characteristics of the patients and details concerning the procedure and the tumor were prospectively recorded.

Treatments

Considering the heavy tumor load in the patients referred to our center, most of them received neoadjuvant chemotherapy and the majority also received adjuvant chemotherapy. Liver resections were performed after complete exploration of the abdominal cavity and with the assistance of an intraoperative ultrasound liver examination. All detectable LM were completely resected during a partial hepatectomy with intermittent vascular exclusion or with radiofrequency ablation (RFA), which was used for small-sized (<2.5 cm) centrally located LM.[18,19] RFA was considered an R1/R0 resection. PM were scored with the peritoneal carcinomatosis index (PCI), which ranges from 1 to 39, and lesions were completely resected with peritonectomy procedures, as described in previous studies.[3,20,21] Macroscopically detectable PM had to be completely resected (i.e., leaving no residual PM exceeding 1 mm in diameter).The microscopic residual PM were then treated perioperatively with intraperitoneal chemotherapy. Intraperitoneal chemotherapy procedures were mostly HIPEC, the remainder being immediate postoperative intraperitoneal chemotherapy.[3,21] In a combined procedure, the liver resection was performed prior to the intraperitoneal chemotherapy.

Patient Groups and Prognostic Factors

The treatment required to guarantee an R0–R1 resection was coded into 3 groups: LR, CCRS–HIPEC, and LR + CCRS–HIPEC. The great variability in outcome due to the tumor load had to be taken into account in order to accurately estimate 5-year survival. After an extensive analysis of the literature, we considered that the main pretreatment prognostic factor for LM was the number of lesions and that the main pretreatment prognostic factor for PM was the PCI. Patients with no PM were coded as having a PCI = 0, and patients with no LM were coded as having 0 liver metastases. The Cox proportional hazards model was used to ensure that these 2 variables were good predictors of survival in our population.

Statistical Analysis

Quantitative variables are described as medians (range) and qualitative variables as percentages. OS was calculated according to Kaplan–Meier from the date of surgery to the date of death. All comparisons are 2-sided and a p value <.05 was used to define statistical significance. All analyses were performed using the R 2.15.2 statistical software.

Design of the Predictive Model A univariate analysis of the effects of variables on survival was performed with a Cox proportional hazard model containing a single variable. When designing a statistical model, it is always necessary to find a trade-off between the accuracy of the predictions and the complexity of the model (i.e., the number of predictors included). More complicated models (with multiple variables) are more accurate but harder to use. Considering the variability in survival observed, our objective was to design a simple nomogram that would be easy to use with a restrained set of variables because very complex scores are rarely used in daily practice. Thus, the gain in precision penalized by augmenting the complexity of the model was estimated with the Akaike Information Criteria and the gain in the C-index. In addition, as the nomogram was intended to be used to help select the best treatment option, no treatment variables (notably preoperative and postoperative chemotherapy) other than surgery were entered in the model. Continuous variables were coded with restricted cubic spline to ensure good accuracy and to relax the linearity assumption.

Nomogram Design The linear predictor of the final Cox model (i.e., the model coefficient multiplied by the value of the variable) and the observed Kaplan–Meier survival were used to design a nomogram predicting survival at 1, 3, and 5 years according to patient characteristics. This part of the analysis was done using the RMS 3.6 package for R (rms: Regression Modeling Strategies, Frank E Harrell Jr., 2012). Nomogram discrimination was evaluated by the bootstrap corrected C-index, which is similar to the area under the ROC curve for censored data. The C-index corresponds to the probability that, in a randomly chosen pair of patients, the one with the highest probability of death given by the model will be the first to die. Calibration was estimated by plotting the mean model-predicted survival and the 95 % CI for 10 groups of patients versus the mean observed survival. When the model is perfectly well calibrated, the predicted probabilities are equal to those observed and therefore located on the diagonal of the diagram. If the calibration is poor, predicted probabilities are far from the those observed and are not reliable.

Use of the Nomogram Nomograms are statistical tools created to help visually determine a probability without complex calculations. In this case, any patient characteristic (the number of metastases, for example) is associated with a number of points that can be read directly on the upper ruler of the nomogram. The points obtained for each characteristic are summed to achieve a total points calculation. In the lower part of the nomogram, total points can then be easily converted into a 1-, 3-, and 5-year predicted survival.

RESULTS

General Characteristics

Between 1995 and 2009, 287 patients with LM, 119 patients with PM, and 37 patients with LM + PM underwent optimal surgery plus chemotherapy (total: 443 patients). Of the 513 potentially resectable patients, 70 (14 %) exhibited disease progressing under neoadjuvant chemotherapy and were excluded for surgery. The main characteristics of these 3 groups of patients are reported in Table 1. Patients having undergone a LR had a median age of 55 years, 88 % had bilateral LM, the median number of LM was 6 (range, 1–42), 61 % had undergone a major hepatectomy, and the median number of RFAs per patient was 2. Patients who had undergone CCRS + HIPEC had a median age of 51 years, a median PCI score of 10 (range 2–36), and a mean number of 3 resected organs per patient (not comprising the omentum, gallbladder, and appendix). Patients having undergone LR and also CCRS + HIPEC had a median age of 49 years, a median number of 2 LM (range 1–16), and a median PCI score of 11 (range 1–26).

Neoadjuvant chemotherapy was administered in 92 % of the 441 patients and adjuvant chemotherapy in 83 %.

Postoperative mortality (until discharge from hospital) was 2.7 % ($n = 5$) after LR, 4.2 % ($n = 5$) after CCRS + HIPEC, and 8.1 % ($n = 3$) after LR with CCRS + HIPEC (NS, $p = .19$), while postoperative grade

TABLE 1 General patient characteristics

Variable	HIPEC ($N = 119$)	HIPEC + LR ($N = 37$)	LR ($N = 287$)
Age (years)[a]	51 (19–71)	49 (22–67)	55 (2–76)
Sex			
Male	49 (41 %)	11 (30 %)	167 (58 %)
Female	70 (59 %)	26 (70 %)	120 (42 %)
N status of primary tumor			
0	19 (16 %)	6 (16 %)	70 (24 %)
1	86 (72 %)	31 (84 %)	170 (59 %)
2	14 (12 %)	0 (0 %)	47 (16 %)
Onset of the metastasis			
Synchronous	66 (55 %)	20 (54 %)	209 (73 %)
Metachronous	53 (45 %)	17 (46 %)	78 (27 %)
Neoadjuvant systemic chemotherapy			
No	10 (8 %)	0 (0 %)	23 (8 %)
Yes	109 (92 %)	37 (100 %)	264 (92 %)
Peritoneal Carcinomatosis Index[a]	10 (2–36)	11 (1–26)	0
Number of invaded areas[a]	6 (1–13)	4.5 (1–13)	NA
Number of LM	0	2 (1–16)	6 (1–42)
Localization of the LM			
Unilateral	NA	22 (63 %)	36 (12 %)
Bilateral	NA	13 (37 %)	251 (88 %)
Major hepatectomy			
No	NA	25 (68 %)	113 (39 %)
Yes	NA	12 (32 %)	174 (61 %)
Radiofrequency ablation			
No	NA	30 (81 %)	83 (29 %)
Yes	NA	7 (19 %)	204 (71 %)
Clavien–Dindo grade III–IV complications			
No	99 (83 %)	22 (59 %)	255 (89 %)
Yes	20 (17 %)	15 (41 %)	32 (11 %)
Postoperative mortality			
No	114 (96 %)	34 (92 %)	279 (97 %)
Yes	5 (4 %)	3 (8 %)	8 (3 %)

NA not applicable, *LM* liver metastasis, *CS + HIPEC* cytoreductive surgery + hyperthermic intraperitoneal chemotherapy

[a] Values depicted are median and range

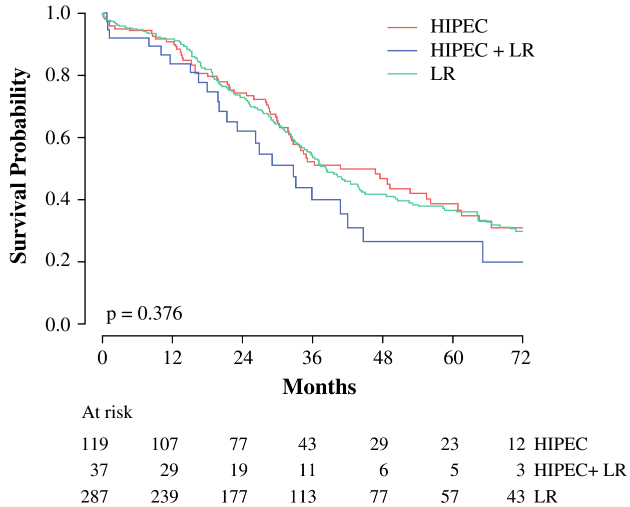

FIG. 1 Overall survival according to patient group. *HIPEC* hyperthermic intraperitoneal chemotherapy, *LR* liver resection

3–4 morbidity was, respectively, 11 % ($n = 32$), 17 % ($n = 20$), and 41 % ($n = 15$) ($p < .001$).

Survival

After a median follow-up of 62.4 months (range 55.6–77.6 months), survival at 1, 3, and 5 years was 90.8 % (range 96.1–85.7 %), 52.2 % (range 62.9–43.3 %), and 38.5 % (range 50.7–29.2 %) in the LR group, 91.4 % (range 94.8–88.2 %), 54 % (range 60.8–48.1 %), 36.5 % (range 43.6–30.5 %) in the CCRS + HIPEC group, and 83.6 % (range 72.4–96.5 %), 43.6 % (range 29.0–65.5 %), 26.4 % (range 13.9–50.3 %) in the LR with CCRS + HIPEC group with no significant difference ($p = .38$) between the 3 groups. Figure 1 shows the OS curves for these 3 groups.

Nomogram

Stratified on the group, both the number of metastases ($p = .037$) and the PCI score (<.0001) were associated with survival. The synchronous onset of metastasis ($p = .62$) and age ($p = .5$) were not associated with survival. On the contrary, gender ($p = .02$), the N status of the primary tumor ($p = .02$), and age ($p < .0001$) were associated with survival in the univariate analysis.

In the multivariate analysis, gender and the N status were marginally associated with survival and added little information based on the Akaike Information Criteria and the C-index and were therefore excluded from the model.

The nomogram derived from the final Cox model is presented in Fig. 2. It uses only 3 criteria: the number of LM, the PCI, and the type of surgery. The bootstrap corrected C-index for the final model was 61 %. Calibration seemed to be correct (Fig. 3) as the predicted survival estimates were close to the observed ones.

DISCUSSION

General Considerations

We undertook this study to help clinicians estimate individualized patient-specific OS with various tumor loads (LM and/or PM) in patients with stage IV colorectal cancers, in whom optimal surgery is technically feasible. We also sought to create a user-friendly clinical decision support tool that uses a limited number of easily and readily obtainable preoperative or intraoperative information to estimate 1-, 3-, and 5-year OS. This assessment tool may facilitate the determination of surgical candidacy for patients presenting with multiple metastatic sites by rapidly assessing long-term survival, even during the operation. The PCI and the number of LM are known during the operation, and a quick and reliable score can help the surgeon decide whether to perform the resection.

To our knowledge, this is the first decision-making tool concerning patients presenting with potentially resectable synchronous LM and PM. Usually, the presence of extrahepatic metastases was a relative contraindication to hepatectomy, just as the presence of LM was a relative contraindication to CCRS + HIPEC. However, recently, a few studies have reported interesting survival results for these contraindicated cases in selected patients.[9–13] Analyzing the prognosis of patients presenting with multiple synchronous metastatic sites is very complex.

Choice of Predictors

The concept of a nomogram combining a simple and internationally recognized score for LM (the number of lesions) and a simple and internationally recognized score for PM (the PCI) enabled us to propose a simple clinical decision aid to the clinician. For both types of metastases, it takes into consideration the best and simplest score reflecting the overall tumor load. It uses a unique prognostic factor (the number of lesions) to assess LM. This point could be criticized, but the number is the most powerful prognostic factor for resected LM in many multivariate studies, when incomplete surgery and the presence of extrahepatic disease are eliminated.[5–7] It uses the PCI, which is also by far the most powerful prognostic factor when incomplete surgery is eliminated.[2–4] Other factors related to the tumor load could have been considered (the size of the metastasis, preoperative carcinoembryonic

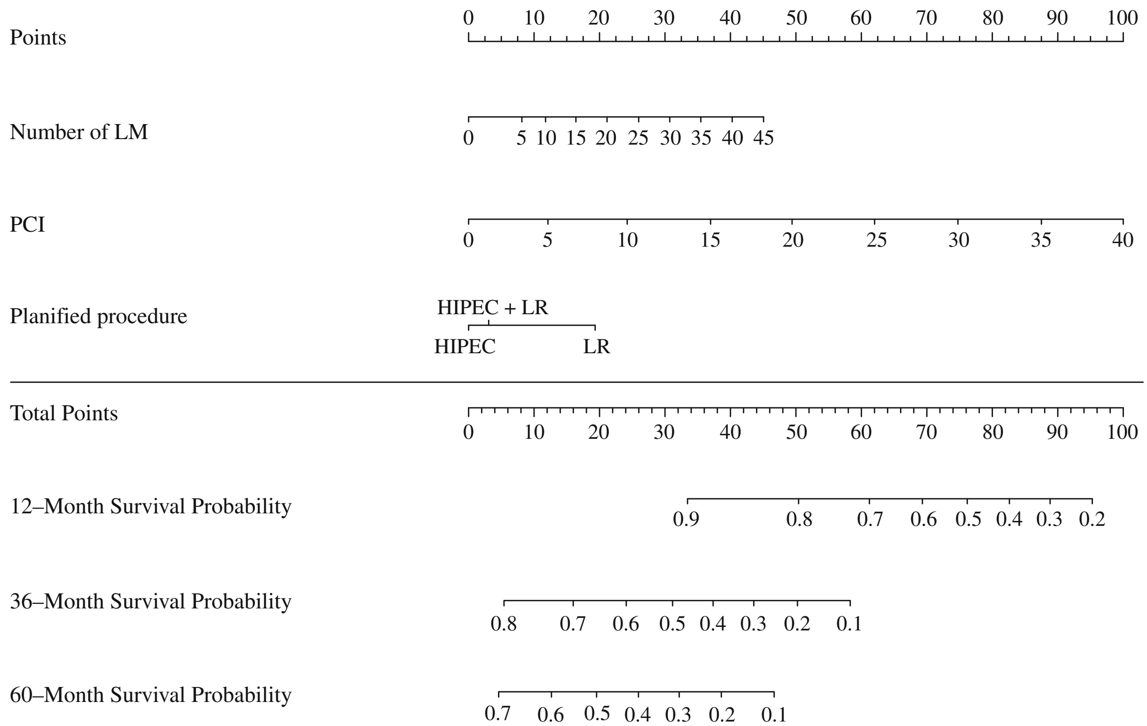

FIG. 2 Nomogram predicting 1-, 3-, and 5-year survival. *LM* liver metastasis, *PCI* peritoneal carcinomatosis index, *LR* liver resection, *HIPEC* hyperthermic intraperitoneal chemotherapy. For example a patient with 5 liver metastases and a PCI of 10 will score (on the *upper ruler*): 7.5 points for the metastasis, 25 points for the PCI, and 2.5 points for the planned procedure resulting in 35 total points. On the lower ruler, the 35 total points predict a 1-year survival rate just below 90 %, 3-year survival rate of between 40 and 50 %, and a 5-year survival rate between 20 and 30 %

antigen [CEA]), but none of them were as easy to estimate and linked to survival as the number of metastases and the PCI score.

Comparison of Predictors

When we compared the assessment of the tumor load according to the number of LM for the liver and according to the PCI for the peritoneum (in other words when patients with LM and patients with PM were compared), the variation in the PCI score seemed to exert a more powerful prognostic impact than the variation in the number of LM, as reported in a recent work by our team.[17] Whereas there is a moderate difference in OS rates between patients with 1–10 LM and patients with >10 LM (respectively, 39.4 and 18.1 % at 5 years), there is a tremendous difference between patients with a PCI score between 1 and 5, and patients with a PCI score ≥16 (respectively, 72.4 and 11.8 % at 5 years).

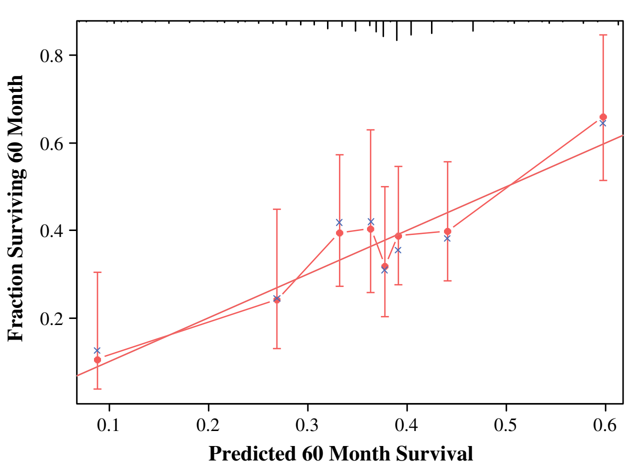

FIG. 3 Calibration curve for survival at 60 months. *Dot* observed *s*

Comparison of Existing Scores and the Nomogram

Other authors have proposed scoring systems to help determine the prognosis. However, scores have 2 major drawbacks. Firstly, scores usually rely on qualitative variables. When you are working with quantitative variables (like the PCI and the number of metastases) they are usually converted into qualitative variables to relax the linearity assumption, but the cutoff points are hard to choose and this results in a loss of information. In nomograms, qualitative variables can be used even if complex transformations are needed. Secondly, scores usually rank patients in categories (i.e., high, medium, low risk), but it is hard to obtain the relationship between the category and the corresponding survival. In nomograms, the total number of points is immediately converted to a predicted 1-, 3-, and 5-year survival rate that provides a lot more information to the clinician.

Justification for a Restricted Number of Predictors

Choosing to evaluate patients with a limited set of predictors has advantages and disadvantages. The main advantage is the simplicity of calculating only 3 parameters that are readily available. This nomogram is therefore far more simple to use than the preoperative nomogram proposed by Beppu et al. which uses 7 risk factors to predict the survival of patients presenting with only LM, or the postoperative nomogram proposed by Kanemitsu et al. on the same subject with 5 risk factors, and also by Kattan et al. with 10 prognostic factors.[5–7] The complexity of their nomograms makes it harder to calculate the estimate, and we believe that complex scores are rarely used in everyday practice. Moreover, most of them use pathologic or postoperative information that is not available during surgery and therefore would not be able to help the surgeon to decide whether or not to perform the surgery.

The main disadvantage is that simple models are not as good as complex ones. Therefore, our survival estimates are less precise than they would have been had we used multiple predictors. Nevertheless, the model achieved a satisfying C-index of 61 % (which is good for censored data) with only 3 predictors, and the calibration curve showed that predicted probabilities were similar to their observed counterparts, meaning that those probabilities were reliable.

Limitations

Our data come from a single tertiary center, and it is also possible that other unknown factors may exist that were not investigated in our previous multivariate studies (data not shown). It should be emphasized that our results were observed in a highly selected population. All patients had a good performance status (ECOG 0–1). Most of them had received preoperative chemotherapy, and progression under chemotherapy was considered a contraindication to surgery. In addition, a safe R0–R1 resection was technically feasible in all of them. These results are therefore not applicable to every patient with PM and/or LM. Finally, we hope that this model will be validated prospectively in other centers in order to be consolidated and to pave the way to formal recommendations for the treatment of this challenging disease.

In conclusion, we present a very simple tool, a nomogram, that allows clinicians to have a preliminary estimation of the OS of patient candidates for optimal surgery for metastases from colorectal cancer (LM, PM, or both).

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