Impact of Neoadjuvant Chemotherapy on Clinical Risk Scores and Survival in Patients with Colorectal Liver Metastases

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ABSTRACT

Background. Several clinical risk scores for patients with colorectal liver metastases (CLM) were established in cohorts of patients undergoing liver resection (LR) without neoadjuvant chemotherapy (NAC). The purpose of the study was to evaluate the predictive values of four common risk scores in the setting of NAC and the impact of score changes during NAC.

Methods. Risk scores (Fong, Nordlinger, Nagashima, and Konopke) were retrospectively calculated for 336 patients undergoing LR for CLM, including 109 patients without and 227 patients with NAC. In patients with NAC, the scores were calculated before and after NAC.

Results. In patients without NAC (n = 109), all risk scores except the Konopke score showed a significant correlation with disease-free survival (DFS). Only the Nagashima score also was predictive for overall survival (OS). In patients with NAC (n = 227), all scores except the Konopke score were predictive for DFS and OS before and after NAC. Score changes in the Fong and the Nagashima score showed a significant correlation with DFS and OS.

Conclusions. Nagashima score was the most universally applicable score and predicted prognosis in all tested scenarios. However, prognosis and outcome are determined by a wide range of patient- and tumor-dependent variables, including tumor size, lymph node positivity of the primary tumor, synchronous metastases, and elevated carcinoembryonic antigen amongst others. To predict prognosis after liver resection of CLM, several clinical risk scores have been developed. The most commonly used scores are the clinical risk score (CRS) by Fong, Nordlinger, Nagashima, and Konopke. All of these scores were established in cohorts of patients undergoing liver resection without prior chemotherapy.

Neoadjuvant chemotherapy (NAC) was introduced to prolong progression-free survival in upfront resectable metastases and to achieve secondary resectability in borderline or nonresectable metastases. NAC is now widely used in clinical practice.

The increasing number of patients receiving NAC might impede the general application of risk scores in the clinical practice. Furthermore, it remains unclear whether a change in risk scores during NAC impacts on survival. To clarify these issues, we analyzed a series of 336 patients undergoing liver resection (LR) for CLM consisting of 227 patients who received NAC and of 109 patients who did not.

MATERIALS AND METHODS

This is a retrospective analysis of 336 patients who underwent liver resection for CLM at our institution from May 2000 to December 2010. Data were extracted from a prospective patient database, laboratory records, and patients charts. The study was approved by the local ethics committee at the Medical University Vienna, Austria. Relevant data for this study included: demographic data, number and size of metastases, primary tumor and lymph
node stage, interval from diagnosis of primary tumor to
detection of metastases, carcinoembryonic antigen (CEA)
levels, resectability of any extrhepatic disease, type of
NAC, as well as overall (OS) and disease-free survival
(DFS).

Patients were divided into two groups depending on
whether they received NAC or not. Easily resectable, small
liver metastases with a good prognosis or patient’s wish
formed the basis of the decision of omitting NAC. Standard
duration of NAC was 3 months in patients with primarily
resectable metastases or until resectability in patients with
initially unresectable CLM. Resectable CLM are defined as
liver metastases, in which upfront R0 resection of all
hepatic lesions is possible, more than 30% estimated
residual liver after resection and disease not in contact with
major vessels of the remnant liver. Clinical scores were
calculated before and after NAC, and change was classified
as decreasing, steady, or increasing scores.

Prognostic Scores

The following scores were calculated and compared: the
CRSs by Fong, Nordlinger, Nagashima, and Konopke2–5.
The detailed description of each CRS is shown in Table 1.
Based on the original publication of Fong et al., we used
the original stratification of two risk groups. All other
scores defined three risk groups2.

### TABLE 1 Clinical risk scores

| CRS criteria (1 point for 1 risk factor) | Risk groups |
|----------------------------------------|-------------|
| Fong                                   |             |
| 1. Largest liver metastasis >5 cm      | Low 0–2 pts |
| 2. Disease free interval <12 months    |             |
| 3. Number of liver metastases >1       | High 3–5 pts|
| 4. Lymph node positive primary tumor   |             |
| 5. CEA >200 ng/ml                      |             |
| Nordlinger                             |             |
| 1. Age >60 a                          | Low 0–2 pts |
| 2. Serosal invasion of primary tumor (≥pT3)| Intermediate 3–4 pts|
| 3. Lymph node positive primary tumor (pN1)| High 5–6 pts |
| 4. Disease free interval <24 months   |             |
| 5. Number of liver metastases >3      |             |
| 6. Largest liver metastasis >5 cm     |             |
| Nagashima                              |             |
| 1. Serosal invasion of primary tumor (≥pT3)| Low 0–1 pts |
| 2. Lymph node positive primary tumor (pN1)| Intermediate 2–3 pts|
| 3. Number of liver metastases ≥2      | High ≥4 pts |
| 4. Largest liver metastasis ≥5 cm     |             |
| 5. Resectable extrhepatic metastases  |             |
| Konopke                                |             |
| 1. Number of liver metastases ≥4      | Low 0 pts   |
| 2. CEA ≥200 ng/ml                     | Intermediate 1 pt |
| 3. Synchronous liver metastases       | High ≥2 pts |

In patients without NAC, scores were calculated before
surgery. In patients with NAC, scores were calculated
before the start of NAC and immediately before liver
resection.

Scores were only calculated when all relevant param-
ters were available. Patients with missing data were
excluded for the respective score calculation. Patients with
NAC were only included in statistical analysis of survival
curves if the clinical risk scores were available for both
time points of evaluation. Furthermore, the differences
between the scores before and after the administration
of NAC were calculated to show if hypothesized prognostic
improvement or decline would cause changes in survival
curves. Any reduction of the score number was classified as
−1, no change as 0, and any increase as +1.

Statistical Analysis

Statistical analysis was performed using SPSS for
Windows, Version 20.0 (SSPS Inc., Chicago, IL). Metric
variables were expressed as mean or median ± standard
deivation. The comparison of variables before and after
NAC was performed by the paired t test if the differences
between the values before and after NAC were normally
distributed. If not, the Wilcoxon signed-rank test was used.
Survival curves were computed with a Kaplan–Meier graph
and compared with the log-rank test. In case of risk scores
with three risk groups, the log-rank test was combined
subsequently with a linear trend test. For comparison of survival curves of patients with a score difference between before and after NAC of $-1$, $0$, or $+1$, the Kaplan–Meier method was combined with a linear trend test. A $p$ value $<0.05$ was considered to indicate statistical significance.

**RESULTS**

A total of 336 patients undergoing liver resection for CLM were included in the study including patients without ($n = 109$) and with NAC ($n = 227$). Patient characteristics are shown in Table 2. The median age of the study population was 63.0 (range, 28–87) years, and the median follow-up was 42.0 (range, 0–140) months. Between patients with and without NAC, no statistically significant difference but a trend towards longer survival in patients without NAC became apparent. Patients without NAC had a longer DFS (14 vs. 9 months, $p = 0.206$) and OS (54 vs. 50 months, $p = 0.584$) than patients receiving NAC.

Patients with NAC had a significantly higher median number of metastases (3 vs. 1, $p < 0.0001$), higher median CEA levels (12.9 vs. 6.8 ng/ml, $p = 0.023$), and suffered more often from synchronous liver metastatic disease (60.7 vs. 40.4 %, $p = 0.0007$). A statistically not significant higher number of pN1 primary tumors (65.6 vs. 56 %; $p = 0.093$) and larger diameters of metastases (4.6 vs. 3.5; $p = 0.116$) could be observed in patients with NAC.

The majority of patients with NAC (81.1 %, $n = 184$) had initially resectable CLM, whereas 18.9 % ($n = 43$) had initially unresectable disease.

Those with initially resectable disease received in 48.4 % ($n = 89$) NAC based on Oxaliplatin, in 10.9 % ($n = 20$) based on Irinotecan, in 36.4 % ($n = 67$) a combination with Avastin, and in 4.3 % ($n = 8$) combination with Cetuximab. Patients with initially unresectable disease received in 30.2 % ($n = 13$) NAC based on Oxaliplatin, in 7.0 % ($n = 3$) based on Irinotecan, in 41.9 % ($n = 18$) a combination with Avastin, and in 20.9 % ($n = 9$) a combination with Cetuximab.

Tumor-specific variables altered in patients with NAC compared with baseline values. There was a significant decrease in the median diameter of metastases (3.5 ± 3.3 cm vs. 2.0 ± 2.9 cm, $p < 0.001$) and in CEA

**TABLE 2** Characteristics of all patients

|                          | All patients ($n = 336$) | Patients without NAC ($n = 109$) | Patients with NAC ($n = 227$) |
|--------------------------|--------------------------|----------------------------------|-------------------------------|
|                          | Value %/Range            | Value %/Range                    | Value %/Range                 |
| Male                     | 214 64/28–87             | 67 33/1–10                       | 88 39/1–10                    |
| Female                   | 122 36/1–10              | 33 2/0.1–0.25                    | 39 3/1–10                     |
| Median age (years)       | 63 28–87                 | 66 41–87                         | 62 28–83                     |
| Primum                   |                          |                                  |                               |
| Colon                    | 221 66/0–4858            | 73 67/0.1–23                     | 148 65/0.1–23                 |
| Rectal                   | 111 33/0.1–23            | 32 30/0.1–23                     | 79 35/0.1–23                  |
| T1                       | 9 3/1–12                 | 2 2/1–10                         | 7 3/1–10                      |
| T2                       | 45 13/0.1–23             | 18 17/0.1–23                     | 27 12/0.1–23                  |
| T3                       | 240 71/0.1–23            | 73 67/0.1–23                     | 167 74/0.1–23                 |
| T4                       | 28 8/0.1–23              | 11 10/1–10                       | 17 8/1–10                     |
| Lymph node positive primary | 202 60/1–10             | 58 53/0.1–23                     | 144 63/0.1–23                 |
| Median CEA (ng/ml)       | 11.1 0–4858              | 6.8 0.7–3800                     | 12.9 0–4858                   |
| Median number of metastases | 2.0 1–12                | 1.0 1–10                         | 3.0 1–12                      |
| Mean diameter of the largest metastasis (cm) | 3.9 0.1–23           | 3.5 0.1–12                       | 4.6 0.1–23                    |
| Synchronous              | 182 54/1–10              | 44 40/0.1–23                     | 138 61/0.1–23                 |
| Metachronous             | 154 46/0.1–10            | 65 60/0.1–23                     | 89 39/0.1–23                  |
| Median DFI (months, 154 patients) | 15 0–180             | 16 1–180                         | 15 0–81                       |
| <12 months               | 229 68/0.1–10            | 64 59/0.1–23                     | 165 73/0.1–23                 |
| <24 months               | 284 86/0.1–10            | 86 79/0.1–23                     | 198 87/0.1–23                 |
| Resectable extrahepatic metastases | 39 12/0.1–23       | 15 14/0.1–23                     | 24 11/0.1–23                  |
| Median OS (months)       | 51 95% CI 42–60          | 54 95% CI 38–70                   | 50 95% CI 38–62               |
| Median DFS (months)      | 10 95% CI 8–12           | 14 95% CI 7–21                    | 9 95% CI 7–11                 |

NAC neoadjuvant chemotherapy, CEA carcinoembryonic antigen, DFI disease free interval, time between resection of primary cancer and diagnosis of liver metastases, OS overall survival, DFS disease-free survival, CI confidence interval
levels (12.7 ± 458.0 vs. 6.6 ± 508.9 ng/ml; \( p < 0.001 \)) after NAC, whereas the median number of metastases remained virtually unchanged (3.0 ± 2.1 vs. 2.0 ± 2.7; \( p = 0.462 \)). During NAC, the diameter of the largest metastases decreased in 71.7 % (\( n = 162 \)), remained the same in 8.4 % (\( n = 19 \)), and increased in 19.9 % (\( n = 45 \)). The CEA level decreased in 58.3 % (\( n = 127 \)), remained the same in 8.7 % (\( n = 19 \)), and increased in 33.0 % (\( n = 72 \)).

Radiological imaging before initiation of NAC showed resectable extrahepatic metastases in 24 patients (10.6 %), whereas intraoperatively resectable extrahepatic metastases were found in 27 patients (11.9 %).

**Predictive Value of Clinical Scores in Patients without NAC**

In patients without NAC, the Fong, Nordlinger, Nagashima, and Konopke scores could be calculated for 106, 103, 103, and 109 patients, respectively. Correlations of the CRSs with DFS and OS for patients without NAC are shown in Table 3. Regarding the prediction of DFS, Fong, Nordlinger, and Nagashima scores were able to show significant differences between the risk groups. However, only the Nagashima score was of predictive value for OS in patients without NAC.

**Predictive Value of Clinical Scores in Patients with NAC**

The Fong, Nordlinger, Nagashima, and Konopke scores could be calculated for 212, 218, 218, and 217 patients, respectively. Correlations of the CRSs with DFS and OS in patients with NAC are shown in Table 3. Before and after NAC, all risk scores showed significant differences in DFS between the risk groups. Before NAC, Fong, Nordlinger, and Nagashima scores were of predictive value for OS. After NAC, all four CRSs showed significant differences in OS between the risk groups.

**Clinical Score Change During NAC**

Overall, score increases during NAC were associated with a worsening in clinical outcome. The scores decreased, and therefore improved, in 27.4 % (\( n = 58 \), Fong) versus 23.9 % (\( n = 52 \), Nordlinger) versus 26.1 % (\( n = 57 \), Nagashima) versus 15.7 % (\( n = 34 \), Konopke). They remained the same in 63.2 % (\( n = 134 \), Fong) versus 67.0 % (\( n = 146 \), Nordlinger) versus 62.8 % (\( n = 137 \), Nagashima) versus 76.0 % (\( n = 165 \), Konopke). They increased in 9.4 % (\( n = 20 \), Fong) versus 9.2 % (\( n = 20 \), Nordlinger) versus 11.0 % (\( n = 24 \), Nagashima) versus 8.3 % (\( n = 18 \), Konopke).
Whereas there was only a trend towards reduced survival in patients with increasing Nordlinger and Konopke scores, decreasing, steady, or increasing Fong and Nagashima scores had significant impact on DFS and OS (Table 4). Kaplan–Meier curves for patients with score changes of the Fong and Nagashima scores during NAC are shown in Figs. 1a–d.

**DISCUSSION**

Several clinical risk scores are used currently in clinical practice to predict prognosis after resection of CLM. Many of these were developed more than a decade ago when NAC was rarely applied in patients with CLM. Today, the consensus guidelines of the European Society for Medical Oncology recommend NAC as current standard in the management of potentially resectable liver metastases. In patients with good prognosis and a single, small (<2 cm) liver metastases upfront surgery may be considered.

The clinical practice guidelines of the National Comprehensive Cancer Network stated that in case of resectable synchronous liver and/or lung metastases only, upfront surgery as well as NAC followed by synchronous or staged colectomy and resection of the metastatic disease is recommended. However, even though the number of patients receiving NAC is increasing, data on the predictive value of CRS in these patients are scarce.

We retrospectively assessed the predictive values of the Fong, Nordlinger, Nagashima, and Konopke scores in patients with and without NAC. The selection of the scores was based on the widespread clinical use of these scoring systems, the easily accessible data required for the calculation of these four scores, and the possibility to compare our findings with a previous study, published by Ayez et al. That study assessed the predictive value of these scores before and after NAC and concluded that the scores are not reliable when used to predict survival before the start of neoadjuvant treatment but are useful when calculated thereafter.

In patients with NAC, they found that only the Nagashima score regarding DFS and only the Nordlinger score regarding OS predicted outcome before and after NAC reliably. A similar study reported that the Fong and the Nordlinger score could not predict OS in the setting of NAC. Regarding the reliability of risk scores in patients without NAC, controversial results were published in the recent literature. Some studies demonstrated the usefulness of the Fong and Nordlinger scores to determine significant differences in DFS and OS. However, another study contradicted these results. Assessments of the Nagashima and Konopke scores regarding their accuracy to predict DFS and OS are rare, but some authors concluded that they seem to be useful tools.

In the study population of Ayez et al., 193 patients received upfront surgery and 159 underwent NAC. In comparison, we could include more patients with NAC but fewer patients without NAC. This might explain why we could observe more significant differences between risk groups in patients with NAC but also might have missed a significant difference in patients without NAC due to a lack of power.

Ayez et al. described a DFS of 9 months [95 % confidence interval (CI) 7–11] and an OS of 47 months (95 % CI 33–61) in patients with NAC. In our study population, similar median DFS (9 months, 95 % CI 7–11) and OS (50 months, 95 % CI 38–62) were observed.

**TABLE 4 DFS and OS in patients with decreasing, steady or increasing scores during NAC**

| DFS median | ≥−1 DFS | 0 DFS | +1 DFS | p value |
|------------|---------|-------|--------|---------|
| Δ Fong (n = 212) | 11.0 (58) | 10.0 (134) | 6.0 (20) | **0.014** |
| Δ Nordlinger (n = 218) | 9.0 (52) | 10.0 (146) | 5.0 (20) | 0.131 |
| Δ Nagashima (n = 218) | 14.0 (57) | 9.0 (137) | 6.0 (24) | **0.012** |
| Δ Konopke (n = 217) | 6.0 (34) | 10.0 (165) | 4.0 (18) | 0.502 |

| OS median | DFS | OS | OS | p value |
|-----------|-----|----|----|---------|
| Δ Fong (n = 212) | 81.0 (58) | 61.0 (134) | 28.0 (20) | **0.004** |
| Δ Nordlinger (n = 218) | 72.0 (52) | 51.0 (146) | 30.0 (20) | 0.109 |
| Δ Nagashima (n = 218) | 65.0 (57) | 61.0 (137) | 33.0 (24) | **0.032** |
| Δ Konopke (n = 217) | 61.0 (34) | 49.0 (165) | 28.0 (18) | 0.194 |

Bold values are statistically significant

DFS disease-free survival, OS overall survival, () n
In patients without NAC, Ayez et al. reported a median DFS of 14 months (95 % CI 11–17) and OS of 43 months (95 % CI 34–52). Our patients without NAC reached a similar median DFS (14 months, 95 % CI 7–21), whereas regarding OS, they performed markedly better (54 months, 95 % CI 38–70). As a reason, we assume that patients with good tumor biology and good prognosis more often underwent upfront surgery in our study population. This selection bias in favor of upfront surgery for patients with favorable tumor biology and good prognosis more often underwent upfront surgery in our study population.

This selection bias in favor of upfront surgery for patients with favorable tumor biology and good prognosis clinical parameters might be a potential limitation of our study. We observed that patients who received NAC had a significantly higher median number and larger diameters of metastases, higher median CEA levels, and suffered more often from synchronous liver metastases and pN1 primary tumors. All of these parameters indicate a more aggressive metastatic disease. It is possible that scores of patients who received upfront surgery due to their good tumor biology are no longer predictive or at least of less predictive value.

A further limitation might be the inherent problem in retrospective analyses that must be taken into account when interpreting the results. However, the large sample size and the long follow-up might outweigh these limitations, particularly regarding the issues that the study was focused on.

Due to consistent accuracy of the Nagashima score through all our patient’s cohorts, it might be the most predictive. In contrast to the Konopke score, which was
rather poorly performing across all our patients, the Nagashima score includes more variables. This probably allows for better patient characterization. Furthermore, patients are distinguished in three risk groups, which is probably more accurate than only two risk groups (Fong score). Indeed, the Nordlinger and the Nagashima score included similar variables and showed similar efficacy regarding overall outcome in our study. However, analyzing score changes during NAC, the Nagashima score was more predictive probably because this score included more changeable parameters than the Nordlinger score.

The assessment of the impact of score changes during NAC showed that only changes of Fong and Nagashima scores were associated with significant differences in survival. A reason for the poorer performance of the other scores might be that none of these CRSs exclusively used changeable parameters for calculation. For example, although the Nordlinger score considers six parameters, only two of them can be influenced by NAC. The Fong score changed in 36.8%, the Nordlinger in 33.1%, the Nagashima in 37.1%, and the Konopke score in 24.0%. Obviously, the Nordlinger and the Konopke are slightly more resistant to the influence of NAC. Additionally, even if parameters change during chemotherapy, this does not mean that they reach the cutoff values leading to score changes. Thus, to improve the impact of clinical scores during NAC on prediction of DFS and OS the use of continuous parameters should be considered.

In our institution, the use of CRSs did not influence the surgical management of CLMs. The process of selecting tailored therapy for each patient is still a goal of interdisciplinary conferences, including surgeons, oncologists, and radiologists. We believe that LR also should be offered to patients with high CRS; however, these patients might benefit from shorter follow-up intervals or an intensified NAC. Thus, further studies are needed to determine the outcome of high-risk patients and liver resection after NAC.

To conclude, only the Nagashima score was able to predict DFS and OS in all patient groups, irrespective of whether calculated before or after NAC. Calculation of changes of the Fong or the Nagashima score can be a valuable tool to estimate the clinical outcome of patients undergoing neoadjuvant treatment.

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DISCLOSURE None.

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