Editorial

Risk of early hepatocellular carcinoma recurrence following liver resection: arbitrary specification or possible target to improve outcome?

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Data from the literature favour liver transplantation (LT) as best curative-intent treatment in patients with early-stage hepatocellular carcinoma (HCC) arising from cirrhosis, as this approach targets both malignancy and the underlying cancerogenic pathomorphology. By strictly adhering to well-defined morphometric tumor burden limits, such as the Milan criteria, excellent recurrence-free survival (RFS) rates beyond 70% at 5 years may be achieved after LT. However, growing donor liver shortage has significantly increased waiting times and thereby risk of tumor-related dropout from the waiting list, ultimately resulting in inferior survival probability. In recent years, this critical situation further aggravated by growing evidence that beyond Milan patients may also benefit from LT, when being successfully downstaged by neoadjuvant locoregional interventions like transarterial chemoembolization (TACE) or radiofrequency ablation (RFA) (1). Therefore, even though being associated with an extraordinary risk of HCC recurrence accounting for 50% to 70%, upfront liver resection (LR) still represents the preferred surgical procedure in patients with resectable tumor stage, especially in those who do not suffer from severe portal hypertension.

In the past two decades, significant advancements were made in hepatic functional evaluation, liver volume preconditioning and minimally invasive surgical techniques, all of whom have contributed substantially in pushing the boundaries regarding morphologic and functional resectability. Ultimately, perioperative morbidity and mortality could be significantly reduced without, however, substantially improving tumor-specific long-term survival (2). Besides stimulating an intensified discussion on most feasible (neo-)adjuvant therapeutical concepts, this contrary outcome trend also led to increasing reflection on the prognostic relevance of post-hepatectomy surveillance. Global guidelines currently recommend follow-up for recurrence every 3–4 months at least during the first year after LR (3). Even though a wide range of time-dependent patient-, tumor- and treatment-related risk factor have been identified in the last years, there is still no general consensus on the most appropriate surveillance strategy during long-term follow-up after hepatectomy (4).

In view of the oncologic threat in times of still lacking well-established adjuvant treatments, follow-up tightening aiming at increasing probability of early detection and curative treatment of recurrent HCC by redo-hepatectomy, LT or RFA appears to be a logical reflection (5). However, respective data are so far not yet conclusive (4,6,7). A recent large Chinese study was not able to identify any survival benefit after shortening of post-LR surveillance interval (2–4 *vs.* 4–6 months) during the first 2 years. In detail, earlier detection did not enhance the chance of a surgical intervention in high-risk patients due to an already advanced stage of intra- and/or extrahepatic relapse, while acceptable prognosis in patients with low-risk tumor

features could thereby not be additionally improved (7).

In a currently presented multicentre study, Yan *et al.* reported on irregular recurrence surveillance (IRS), as defined by follow-up interval beyond 6 months or symptomatic HCC recurrence, as a significant prognostic factor in 1,426 HCC patients following hepatectomy. Median post-resection survival was 32.1 months in patients under regular recurrence surveillance (RRS; every 2–3 months for the first 24 months, and every 6 months afterwards) but only 21.2 months in those following IRS. Moreover, IRS turned out to be an independent predictor of poor post-recurrence survival, along with other well-established risk factors, such as elevated serum alfa-fetoprotein (AFP), extrahepatic spread, beyond Milan status, curative-intent option and early (within 24 months) recurrent HCC (8). This was an important finding, which could have significant impact on postoperative surveillance strategy and persistence, since it suggests consequent adherence rather than undifferentiated intensification of a well-defined follow-up schedule. Notably, the authors reported on a significantly higher proportion of RRS in the early (79.8%) *vs.* late (45.1%) recurrence subset of patients, which at first glance, appears to be incomprehensible, since relapse soon after LR was in the past clearly shown to be associated with aggressive tumor biology and inferior outcome. But although the prognostic impact of RRS in this specific subgroup has not been analysed in detail by Yan *et al.*, this finding may be interpreted as an indirect reference for urgent need of effective adjuvant treatments particularly in the early postoperative period, as close surveillance alone does not seem to be effective in improving RFS in high-risk patients.

In contrast, respective data in low-risk patients seem to be more consistent. Noteworthy, another recent multicenter study was able to identify RRS as an independent protective factor in a subset of 303 HCC patients suffering from late (beyond 24 months) HCC relapse, particularly triggered by a significantly higher rate of curative-intent treatment modalities applied (9). Given a not uncommon decline of patients' compliance in the context of an uneventful early clinical course, data of these two studies may be used as an appeal for a consequent continuation of an established surveillance program especially in post-hepatectomy periods which are generally characterized by a lower oncologic risk.

Basically, Yan *et al.* emphasized on the predictive role of time to recurrence as a surrogate marker of biological tumor aggressiveness and outcome in the setting of LR. Comparable to previous investigations (4,6,7), the authors demonstrated early HCC recurrence (within 24 months) to be associated with a significantly higher probability of beyond Milan extent and extrahepatic manifestation, which in turn, was resulting in a lower likelihood for indicating surgical intervention and thereby higher cancer-specific mortality as compared to late (beyond 24 months) relapse patients (8). In fact, a threshold of 2-year is currently widely accepted to distinguish between two different post-hepatectomy risk periods and associated needs with regard to surveillance intensity and adjuvant treatments discussed. Based on differential clinicopathologic risk profiles and genomic tumor origin, occult intrahepatic micrometastasis mediated by portal perfusion is thought to be the major mechanism of more aggressive early ("true") recurrence, while multicentric occurrence resulting from *de novo* hepatocarcinogenesis in the context of background liver damage was identified to account for more favourable late HCC relapse pattern. However, this stringent cut-off is increasingly considered arbitrary, and other study groups have proposed different thresholds ranging from 8 months to 5 years (10,11). There is convincing evidence that determination of overall recurrence risk may not adequately describe postoperative dynamics of the oncologic risk. Recent chronological studies demonstrated post-resection recurrence hazards and peaks to vary substantially depending on clinicopathologic risk factors and post-LR time point. In a long-term study of 1,918 HCC patients following hepatectomy, Kim *et al.* reported on a relapse peak of 21.7% during the first year, which was gradually decreasing through 5 years, followed by stabilized oncologic risk <7% until year 10. Apart from that, AFP level, features of biological aggressiveness (size and number, microvascular and capsular invasion) and higher METAVIR fibrosis stage were independently associated to disease recurrence within 5 years, while METAVIR F4 cirrhosis alone remained as independent prognostic factor of beyond 5-year relapse (11). Thus, adherence to a well-defined surveillance program also well beyond the recommended 2-year cut-off in case of aggressive HCC phenotype may be essential. Even though not being based on a time-dependent analysis, the study by Yan *et al.* seems to finally confirm this conclusion, as they observed a series of similar cancer-related features to independently predict both early and late HCC recurrence (8).

In addition, the predictive role of background liver disease should be re-considered in this specific context, as chronological analyses consistently revealed histological severity of underlying pathomorphology and related hepatic functional impairment rather than cirrhosis as a dichotomous variable to correlate with tumor-specific outcome. Even more

important, cirrhosis-related carcinogenesis became not only evident in later postoperative stage, which is predominantly dominated by multicentric tumor recurrence, but may also affect early risk of true HCC relapse (4,11,12). Besides undetected intrahepatic metastasis at the time of hepatectomy, circulating tumor cells perioperatively released by primitive HCC via micro- and/or macro-angioinvasion are meanwhile considered to be another important seed of early HCC relapse. Even though the biological processes of intrahepatic tumor cell re-homing and growth are still largely unexplored, pro-inflammatory and immunosuppressive mechanisms were shown to play a pivotal role in systemic HCC recurrence, which, in turn, may be substantially aggravated by progressive cirrhosis and functional deterioration (4,13).

Chronological re-evaluation of intrinsic and extrinsic cancerogenic risk factors appears to be crucial for refining individual risk estimation, optimizing surveillance and improving long-term outcome post-hepatectomy. In a long-term follow-up study including 2,523 HCC patients, Cucchetti *et al.* recently demonstrated an increasing likelihood of being cured with passing of post-LR RFS (14). Despite development of novel and more tolerable immunotherapeutic agents, background cirrhosis in the remnant liver remains a limiting factor for realizing effective adjuvant therapies. In addition, it represents a persistently acting tumor-promoting factor of systemic HCC recurrence and *de-novo* hepatocarcinogenesis. Probably, greater emphasis should therefore be placed on re-implementation of well-established neoadjuvant locoregional interventions. In this context, the primary goal should not only be to increase resectability by tumor downsizing, but rather to reduce risk of perioperative cancer cell spread via angioinvasion, in order to delay potential recurrence into post-hepatectomy periods, whose hazard potential is mainly determined by background cirrhosis and not by intrinsic aggressive tumor phenotype (15).

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