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First Long-term Oncologic Results of the ALPPS Procedure in a Large Cohort of Patients With Colorectal Liver Metastases

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Objectives: To analyze long-term oncological outcome along with prognostic risk factors in a large cohort of patients with colorectal liver metastases (CRLM) undergoing ALPPS.

Background: ALPPS is a two-stage hepatectomy variant that increases resection rates and R0 resection rates in patients with primarily unresectable CRLM as evidenced in a recent randomized controlled trial. Long-term oncologic results, however, are lacking.

Methods: Cases in- and outside the International ALPPS Registry were collected and completed by direct contacts to ALPPS centers to secure a comprehensive cohort. Overall, cancer-specific (CSS), and recurrence-free (RFS) survivals were analyzed along with independent risk factors using Cox-regression analysis.

Results: The cohort included 510 patients from 22 ALPPS centers over a 10-year period. Ninety-day mortality was 4.9% and median overall survival, CSS, and RFS were 39, 42, and 15 months, respectively. The median follow-up time was 38 months (95% confidence interval 32–43 months). Multivariate analysis identified tumor-characteristics (primary T4, right colon), biological features (*K/N-RAS* status), and response to chemotherapy (Response Evaluation Criteria in Solid Tumors) as independent predictors of CSS. Traditional factors such as size of metastases, uni versus bilobar involvement, and liver-first approach were not predictive. When hepatic recurrences after ALPPS was amenable to surgical/ablative treatment, median CSS was significantly superior compared to chemotherapy alone (56 vs 30 months, $P < 0.001$).

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Conclusions: This large cohort provides the first evidence that patients with primarily unresectable CRLM treated by ALPPS have not only low perioperative mortality, but achieve appealing long-term oncologic outcome especially those with favorable tumor biology and good response to chemotherapy.

Keywords: associating liver partition and portal vein ligation for staged hepatectomy, cancer-specific survival, colorectal liver metastases, long-term outcome, tumor biology

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The liver is the most common organotropic site for distant metastases from colorectal cancer.[1] Often, patients with colorectal liver metastases (CRLM) present with extensive hepatic disease, which are not amenable to curative one-stage resection due to bi-lobar involvement and/or a too small future liver remnant (FLR). In these upfront unresectable scenarios, neoadjuvant chemotherapy followed by two-stage hepatectomy (TSH) offers a potential curative strategy.[2–4]

Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) is a TSH variant triggering rapid FLR hypertrophy that enables two-stage completion within a short period of 7 to 14 days.[5] ALPPS increases resection rates and R0 resection rates and has been mainly performed for otherwise unresectable CRLM.[4,6,7] In addition, a recent randomized controlled trial revealed superior resection rates and overall survival over the classical TSH approach in patients with CRLM.[8,9] Although initial reports of ALPPS raised safety concerns of high morbidity and early mortality rates,[7,10] there is accumulating evidence that perioperative mortality has meanwhile improved for this complex procedure to the level of comparable results associated with major hepatectomy.[7]

Although CRLM remain the main indication for ALPPS among all liver tumors, long-term oncologic results are still lacking, and are nowadays considered as the Achilles' heel of ALPPS. Therefore, the goal of the present study was to fill the gap of missing long-term outcome data in a large cohort of patients undergoing ALPPS for CRLM. In addition, the study aims to identify independent predictors of long-term oncological outcome.

MATERIAL AND METHODS

Study Design

This ALPPS cohort study follows an international, multicenter design and is based on data captured in and outside the International ALPPS Registry (ClinicalTrials.gov: NCT01924741). The Registry prospectively collects data on ALPPS cases since 2012 and is coordinated by the Department of Surgery, University of Zurich, Switzerland. In addition, centers outside the ALPPS registry were contacted to contribute cases retrospectively. ALPPS centers contributing 10 or more cases to the ALPPS Registry as well as ALPPS centers outside the registry with an experience of the same threshold volumes were considered for study enrollment. Demographic, tumor-related, and survival data were collected. The primary objective of this study was to investigate factors determining long-term cancer-specific survival (CSS) of patients undergoing ALPPS for CRLM. All participating centers were directly contacted to close data gaps and update their cases with the most recent follow-up per February 09, 2020. The Cantonal Ethics Committee of Zurich approved to use registry data for scientific analysis (KEK 2013–0326). Furthermore, the Scientific Committee of the ALPPS Registry approved the current study on June 27, 2017 (http://alpps.net/?q=node/90). Approval to use data of additional cases for this multicenter analysis was obtained by the local institutional review boards of the respective centers.

Grouping of Right- Versus Left-sided Primary Colon Tumor

The anatomic localization of the primary colorectal cancer was group into right- and left-sided colonic tumors. Left colonic and rectal tumors were grouped as left-sided tumors. Patients with concomitant right- and left-sided tumors were assigned to the right-sided group. Transverse colon tumors were assigned to left- and right-sided by the center without providing the exact anatomic demarcation line. Although the majority of studies uses the splenic flexure as demarcation line between right- and left-sided tumors,[11] the low incidence of transverse colonic tumors of approximately 5% among all colorectal tumors would make a misclassification into right- or left-sided group statistically negligible.[12]

Assessment of Response to Chemotherapy

Response to chemotherapy before ALPPS was assessed by serum carcinoembryonic antigen (CEA) levels, image-based tumor morphology, and pathological-based microscopic evaluation. Serum CEA levels were collected before and after pre-ALPPS chemotherapy and the drop in percent was calculated. Imaging-based response to chemotherapy was assessed by unidimensional measurement of the target lesions using the Response Evaluation Criteria in Solid Tumors (RECIST).[13] Good response was defined as complete or partial response whereas poor response as stable or progressive disease. Pathology-based response to chemotherapy was graded using the 5-graded tumor regression classification system.[14]

Definition of Survival Endpoints

The primary endpoint was CSS, which was defined as time from ALPPS stage 1 to death from underlying colorectal cancer disease excluding patients with 90-day mortality. Secondary survival endpoints included overall survival (OS, time from ALPPS stage 1 to death of any cause) and recurrence-free survival (RFS, time from ALPPS stage 1 to occurrence of recurrent disease). Patients without documented event (death or recurrence) were censored and marked in the respective plots.

Statistical Analysis

For descriptive statistics and univariate analysis continuous data are reported as median and inter-quartile range, categorical data are reported as frequencies and proportions in percentage (%). In univariate analysis, OS, CSS, and RFS were compared among various patients and tumor characteristics as well as individual response to chemotherapy. Receiver operating characteristics curve analysis was performed to identify the optimal cut-off points for continuous variables. Briefly, this was based on the Youden *J* statistic, which gives equal weight to sensitivity and specificity. Primary and secondary survival endpoints were analyzed by the Kaplan-Meier method and groups were compared with the log-rank test. Multivariable analysis was performed with Cox regression analysis. Cases with missing data were excluded from Kaplan-Meier survival and multivariable analysis. All *P*-values were two-sided and considered statistically significant if $P \leq 0.05$, unless stated otherwise, in the multivariable analysis where $P \leq 0.1$ was considered statistically significant. Statistical analysis was performed using R version 3.3.2, R Studio version 1.0.44 (Boston, MA, 2016) with the graphical user interface rBiostatistics.com alpha version (rBiostatistics.com, London, UK, 2017) and IBM SPSS Statistics version 22 for Macintosh (IBM Corporation, Armonk, NY).

RESULTS

How Was the Study Population Composed?

The cohort included 510 patients with CRLM who underwent ALPPS during the 10-year period from 2009 to 2019 from 22 international centers. The median age of the entire cohort was 60 years (51–67 years) and 64% of patients (n = 326) were male. The majority of patients presented with synchronous (74%) and bilobar (81%) disease and underwent neoadjuvant chemotherapy (92%) before ALPPS. The median number of liver lesions was 6 (4–10) with a median diameter of the largest lesion of 45 mm (30–70). The vast majority of patients (96%) completed stage 2 surgery. The 90-day mortality rate after ALPPS was 4.9%. At time of the last follow-up, 121 patients were alive without disease, 129 alive with disease, 177 died due cancer, 44 died due other causes, and patient status was unknown in 39 patients. The median follow-up time was 38 months [95% confidence interval (CI) 32–43 months]. Detailed information on patient, tumor, and treatment characteristics as well as survival are presented in Table 1 and Figure 1.

Did Surgical Strategy or Postsurgical Complications Influence Oncological Outcome?

Overall, the ''classical'' ALPPS procedure was performed in 66% of cases, whereas less invasive variants were performed in 34% of cases (Table 2). The choice of the procedure variant did not affect CSS ($P = 0.99$). Likewise, the liver-first versus primary tumor-first approach did not affect CSS ($P = 0.467$). In contrast, patients developing major complications (Clavien-Dindo $\geq$3b) were associated with significantly lower median CSS as compared to patients without major complications, 31 (26–35) versus 45 (39–51) months, $P = 0.006$) (Supplementary Fig. 1, http://links.lww.com/SLA/C447). When an early period (2008–2014) was compared with a later period (2015–2019), we found a significant shift to more less-invasive stage 1 procedures and liver-first approaches as well as less postoperative complications (Supplementary Tables 1 and 2, http://links.lww.com/SLA/C447).

What Was the Impact of Traditional and Biological Tumor Characteristics?

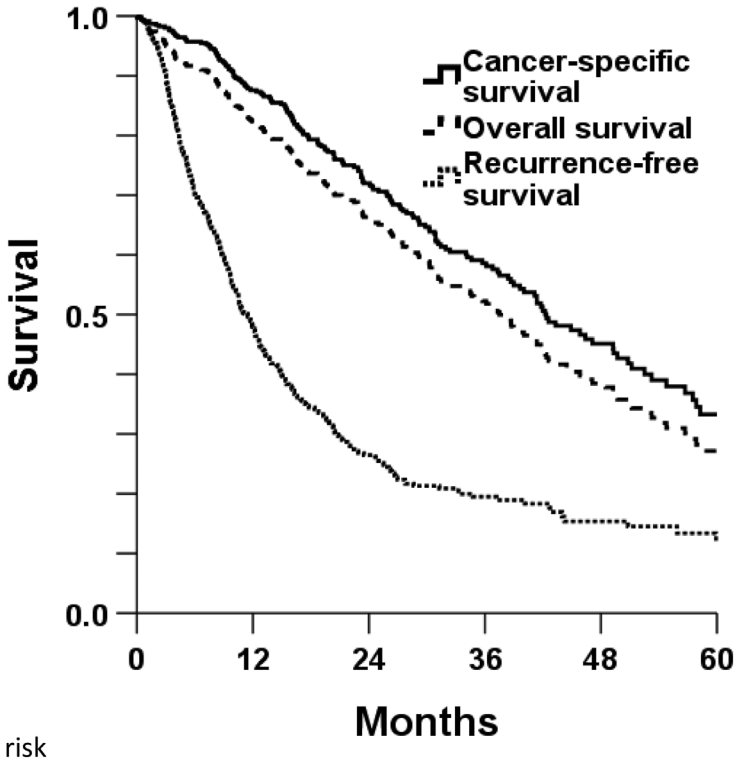
Univariate and Kaplan-Meier survival analysis demonstrated that age greater 67 years, right colon localization of primary tumor,

TABLE 1. Patient and Tumor Characteristics

Variable	Number of Patients	Data Completion	Value
Age, yrs	510	100%	60 (51–67)
Gender; female, n (%)	510	100%	184 (36)
BMI, kg/m^2	479	94%	25 (23–28)
Primary tumor			
Location of primary tumor	497	97%	
Right colon, n (%)			107 (36)
Left colon, n (%)			206 (41)
Synchronous right and left colon, n (%)			7 (1)
Rectum, n (%)			177 (36)
T1/T2/T3/T4, n (%)	459	90%	9 (2)/46 (10)/298 (65)/106 (23)
N0/N1/N2, n (%)	459	90%	106 (23)/184 (40)/169 (37)
Liver metastases			
Concomitant lung metastases, n (%)	453	89%	40 (9)
Timing of liver metastases	500	98%	
Synchronous, n (%)			369 (74)
Metachronous, n (%)			131 (26)
Bilobar disease, n (%)	500	98%	403 (81)
Number of lesions, n	446	87%	6 (4–10)
Diameter of largest lesion, mm	469	92%	45 (30–70)
Liver-first approach, n (%)	500	98%	109 (22)
K/N-RAS	425	83%	
Mutated, n (%)			162 (38)
Wild type, n (%)			263 (62)
CEA before chemotherapy, μg/l	310	61%	53 (12–208)
CEA before ALPPS, μg/l	288	56%	10 (3–35)
Chemotherapy			
Chemotherapy before ALPPS, n (%)	499	98%	457 (92)
Monoclonal Antibodies, n (%)	472	93%	317 (67)
Chemotherapy response (RECIST)	449	88%	
RECIST 0–1, poor response, n (%)			139 (31)
RECIST 2–3, good response, n (%)			310 (69)
Chemotherapy response (Path)*, n (%)	319	63%	
TRG 1, no residual cancer, n (%)			40 (13)
TRG 2, rare residual cancer, n (%)			83 (26)
TRG 3, residual cancer < fibrosis, n (%)			97 (30)
TRG 4, residual cancer > fibrosis, n (%)			88 (28)
TRG 5, no signs of regression, n (%)			11 (3)

*Refers to tumor regression according to Rubbia Brandt.[14] Continuous variables presented as median (inter-quartile range). Categorical variables presented as count and percent (%).

ALPPS indicates associating liver partition and portal vein ligation for staged hepatectomy; BMI, body mass index; CEA, carcinoembryonic antigen; CRLM, colorectal liver metastases; RECIST, response evaluation criteria in solid tumors; TRG, tumor regression grade.



No at risk						
CSS	468	341	208	116	58	24
OS	468	341	208	116	58	24
RFS	465	190	80	36	19	8

FIGURE 1. Short- and long-term survival outcomes after ALPPS for the entire cohort. Kaplan-Meier plots for CSS, OS, and RFS. Median CSS, OS, and RFS were 42, 37, and 11 months. Three- and 5-year CSS, OS, and RFS were 59%, 52%, and 19% and 33%, 27%, and 12%. CSS indicates cancer-specific survival; OS, overall survival; RFS, recurrence-free survival.

T4 stage, presence of positive lymph nodes (N1/2), more than 7 liver lesions, and *K/N-RAS* mutation were associated with reduced CSS. The greatest survival difference was observed for the *K/N-RAS* status where median and 5-year CSS was 49 months and 41% for wild-type versus 34 months and 11% for mutated tumors (Fig. 2F). The impact of *K/N-RAS* mutation on survival after ALPPS was documented for both right- and left-sided primary tumors but was more pronounced in patients with right-sided tumors (Supplementary Fig. 2, http://links.lww.com/SLA/C447).

How did Response to Chemotherapy Correlate With Cancer-specific Survival?

Response to chemotherapy was assessed by three different elements of serum tumor marker (CEA), morphological (RECIST), and pathological (tumor regression grade) response. Data on RECIST were available in 449 patients, tumor regression grade in 320, and CEA levels in 310. CSS was significantly superior for patients who responded to neoadjuvant chemotherapy for all 3 tumor response elements (Fig. 2G–I). For instance, median CSS for patients with RECIST complete or partial response was 51 months (95%CI 41–61) compared to 30 months (95%CI 21–35) in patients with stable or progressive disease. Patients who responded by morphological or pathological criteria had significantly greater drops in serum CEA levels after neoadjuvant chemotherapy (Supplementary Fig. 3, http://links.lww.com/SLA/C447).

Which Independent Risk Factors Were Associated With Cancer-specific Survival?

Only variables presenting preoperative information were included in the multivariate analysis. Finally, 9 variables, which proved to be significant at $P \leq 0.1$ in the univariate analysis, were included in the Cox regression analysis. Poor response to chemotherapy defined by RECIST (adjusted Hazard ratio [aHR] 2.30), presence of *K/N-RAS* mutation (aHR 1.68), localization of primary tumor in the right colon (aHR 1.55), and T4 stage (aHR 1.51) independently predicted reduced CSS (Fig. 2J).

How Was Hepatic Recurrence Managed After ALPPS?

At time of last follow-up, 71% of patients (n = 343) experienced recurrent disease while 29% (n = 140) did not, and approximately 80% of patients experienced recurrent disease within the first 3 years after ALPPS (Fig. 1). Recurrent metastatic disease was most frequently localized in the liver (60%) followed by lungs (43%), peritoneum (19%), and other organs (6%) (Fig. 3A). Median CSS was significantly better for patients with recurrent liver disease, who were complementary treated by surgery and/or ablation compared to those treated by chemotherapy only (56 vs 30 months) (Fig. 3B). The group with complementary surgery and/or ablation were younger and had a lower proportion of right primary tumor localization and *K/N-RAS* mutations.

DISCUSSION

This large cohort study fills the gap of missing oncological long-term outcome data in patients undergoing ALPPS for extensive CRLM. The study results demonstrate that favorable tumor characteristics including tumor biology and disease control by chemotherapy were the most important elements to secure excellent long-term survival. Of note, unfavorable response to chemotherapy was associated with the highest risk of poor prognosis among all independent risk factors.

TABLE 2. Surgery and Outcome Characteristics

Variable	Number of Patients	Data Completion	Value
ALPPS procedure	501	98%	
Classic ALPPS, n (%)			331 (66)
Less invasive ALPPS, n (%)			170 (34)
Rescue ALPPS, n (%)	323	63%	25 (8)
sFLR stage 1	265	52%	0.20 (0.15–0.26)
sFLR stage 2	300	59%	0.33 (0.20–0.46)
sFLR increase (%)	272	53%	64 (12–109)
Cleaning of FLR at stage 1, n (%)	319	63%	204 (64)
Concomitant colorectal resection stage 1, n (%)	313	61%	204 (64)
Interstage interval, days	468	92%	13 (9–21)
Stage 2 performed, n (%)	510	100%	492 (96)
R0 Resection at stage 2, n (%)	302	59%	220 (73)
Mortality and complications			
90-day mortality, n (%)	510	100%	25 (5)
Any complication stage 1, n (%)	302	59%	166 (55)
Any complication stage 2, n (%)	300	59%	192 (64)
Complications ≥3b stage 1, n (%)	501	98%	37 (7)
Complications ≥3b stage 2, n (%)	485	95%	100 (21)
Recurrence			
Recurrence, n (%)	483	95%	343 (71)
Liver recurrence, n (%)	442	87%	267 (60)
Extrahepatic recurrence, (%)	426	84%	255 (60)
Lung, n (%)			184 (43)
Peritoneum, n (%)			82 (19)
Bone, n (%)			13 (3)
Nervous system, n (%)			12 (3)
Local (CRC), n (%)			7 (2)
Adrenal gland, n (%)			6 (1)
Other, n (%)			54 (13)
Treatment of recurrence			
Chemotherapy, n (%)	348	68%	253 (73)
Surgery, n (%)	337	66%	70 (21)
Ablation, n (%)	322	63%	46 (14)
Other*, n (%)	289	57%	20 (7)

*Refers to liver transplantation, radiation, TACE and SIRT. Continuous variables presented as median (inter-quartile range). Categorical variables presented as count and percent (%).

ALPPS indicates associating liver partition and portal vein ligation for staged hepatectomy; CRC, colorectal cancer; sFLR, standardized future liver remnant; SIRT, selective internal radiation therapy; TACE, transarterial chemoembolization.

Patients with unresectable CRLM, who are candidates for two-stagey hepatectomy, either by ALPPS or conventional TSH, need to be embedded in an oncological treatment strategy.[15] This strategy requires taking into account the syn- and metachronous timing of CRLM as well as the extent of hepatic and extrahepatic disease. Regardless of the recommended individual treatment sequence,[16] all ALPPS candidates nowadays should undergo neoadjuvant chemotherapy to study the natural behavior of the disease and, more importantly, control the disease before surgery. In our study, almost every patient received upfront chemotherapy before ALPPS, which is also in line with the same neoadjuvant strategy reported for patients with CRLM in the setting of conventional TSH.[3,17,18]

The hallmark finding of the study was that response to neoadjuvant chemotherapy was the strongest independent predictor of short- and long-term oncological outcome among all analyzed risk factors. We have demonstrated that favorable tumor marker (CEA), morphological (RECIST) as well pathological response (tumor regression grade) to chemotherapy translated in significantly improved survival after ALPPS, which has been also reported for other types of liver surgery in CRLM.[19–21] The advantage of the variable ''tumor response to chemotherapy'' relates to its dynamic character unlike static variables such as *K/N-RAS* mutation status or localization of the primary colon tumor. Although all 3 response parameters were significantly associated with CSS in our univariate survival analysis, we included only morphological response in the multivariate analysis due to the potential confounding nature among the variables.

Another central finding of the study highlights the importance of tumor biology, which is presented by 3 independent risk factors of reduced survival after ALPPS including T4 stage, right-sided localization of the primary colon tumor, and *K/N-RAS* mutation. Especially, the tumor intrinsic factor *K/N-RAS* had the strongest impact on oncological outcome among all static tumor variables. The negative prognostic impact of *K/N-RAS* mutations on survival in our series parallels observations repeatedly reported for one-stage resections,[22–24] conventional TSH,[25] and ALPPS.[26] Of note, *K/N-RAS* mutated tumors represent the largest proportion among the 7 colorectal cancer molecular subtypes.[27]

Oncological behavior of colorectal cancer has been linked to the anatomical localization of the primary tumor.[28] In general, right-sided tumors have a more aggressive behavior and differ in molecular characteristics compared to left-sided tumors.[27] Despite the therapeutic regimens being different between primary left colonic and rectal cancers, both entities were grouped into a left-sided category according to previous studies.[29,30] Numerous studies confirmed that right-sided colon tumors are associated with worse prognosis after hepatic metastasectomy.[23,29,30] This prognostic relationship has been observed in the present ALPPS cohort as well, where right-sided primary tumors were associated with a worse prognosis after ALPPS. In addition, the study found that the impact of *K/N-RAS* mutations is even worse in

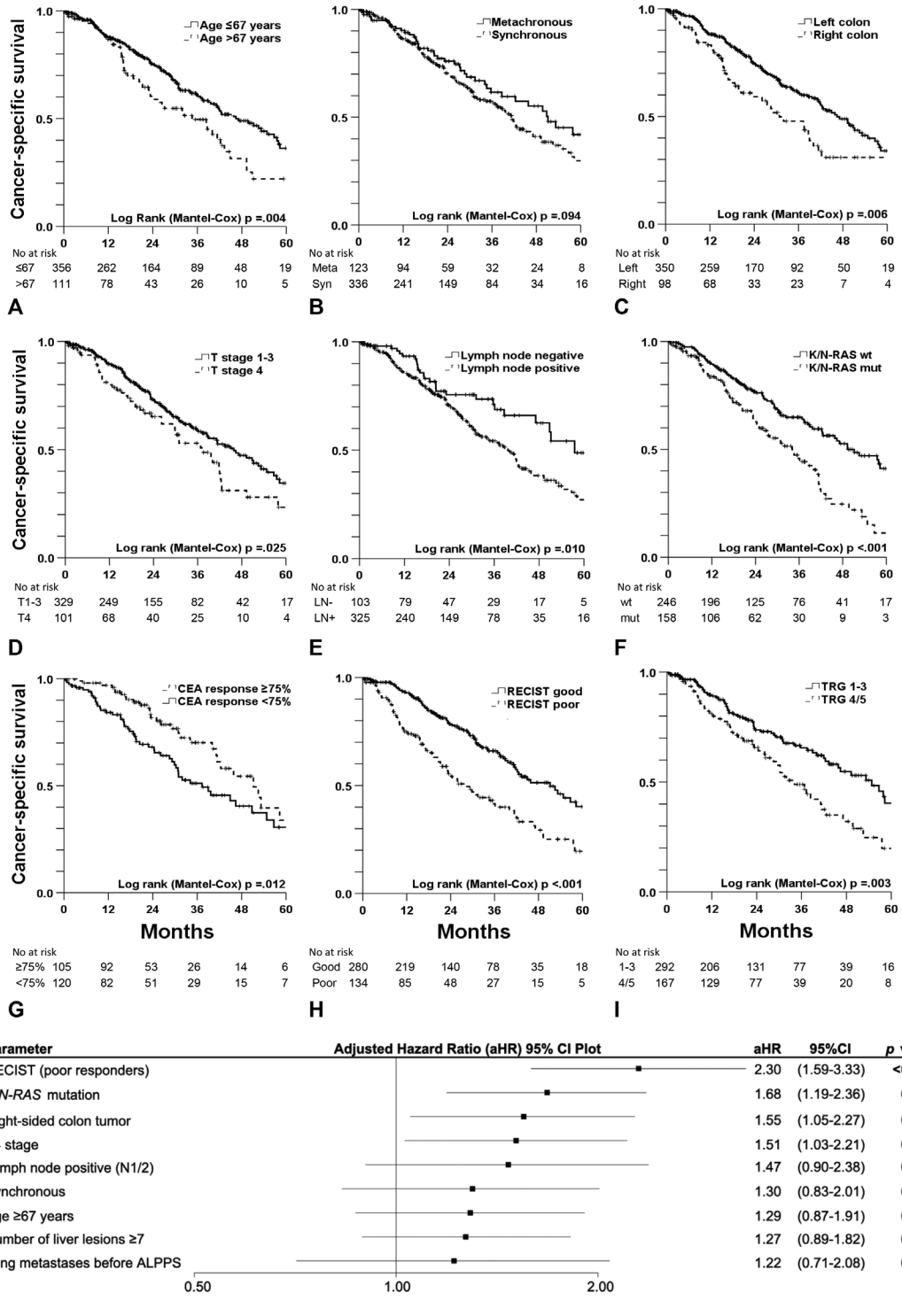


FIGURE 2. Preoperative factors associated with CSS in uni and multivariate analysis. Panels A–I illustrate Kaplan-Meier CCS plots for (A) age ($\leq$67 vs $>$67 years), (B) timing of liver metastases (syn vs metachronous), (C) localization of primary tumor (right vs left colon), (D) T stage (T1/2/3 vs T4), (E) lymph node metastasis (N0 vs N1/2), (F) *K/N-RAS* status (wild-type vs mutation), response to neoadjuvant chemotherapy using (G) serum CEA levels before and after neoadjuvant chemotherapy (drop in CEA $\geq$75% vs $<$75%), (H) Response Evaluation Criteria in Solid Tumors (good vs poor) and (I) tumor regression grade (1/2/3 vs 3/5). Survival groups were compared using the log-rank (Mantel Cox) test. Panel J presents the multivariate Cox regression analysis for CSS with 323 patients. Adjusted Hazard ratio plots are presented with the 95% confidence interval for significant and nonsignificant risk factors. RECIST good is defined as complete or partial response while RECIST poor as stable or progressive disease. CEA indicates carcinoembryonic antigen; CSS, cancer-specific survival.

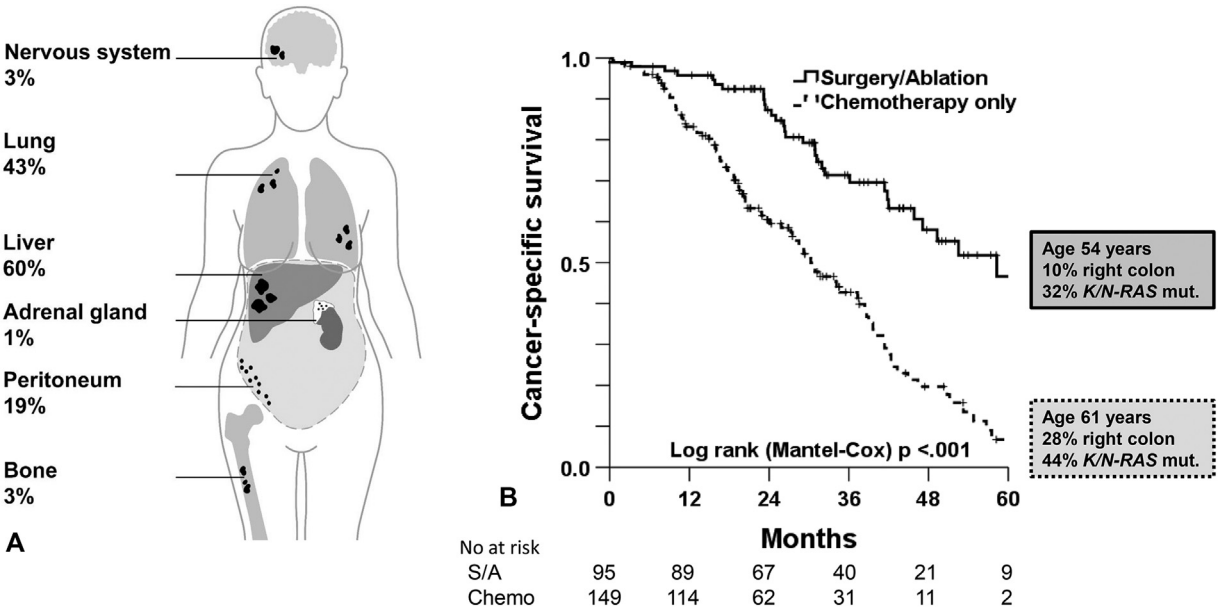


FIGURE 3. (A) Pattern und distribution of metastatic recurrence after associating liver partition and portal vein ligation for staged hepatectomy. (B) Cancer-specific survival of patients with recurrent metastatic disease managed by chemotherapy only or complementary by surgery and/or ablation. The group with complementary surgery and/or ablation were younger and had a lower frequency of right-sided primary colon tumors and *K/N-RAS* mutations compared to the group managed by chemotherapy only for recurrent disease.

right- compared to left-sided tumors. However, the importance of *K/N-RAS* and primary tumor localization does not only apply to the prognosis after ALPPS but also to the individualized chemotherapy regimen.[27]

The set of identified independent risk factors not only underlines the importance of tumor biology and response to chemotherapy but also highlights the personalized character of oncological prognosis after ALPPS. These risk factors might help to guide appropriate selection of patients with unresectable CRLM, who are considered for ALPPS. In other words, patients who progress under neoadjuvant chemotherapy and harbor an additional *K/N-RAS* mutation should not be considered for ALPPS.

Surprisingly, traditional factors such as size of liver metastases, bilobar disease, or even concomitant lung metastases before ALPPS had no significant impact on oncological outcome after ALPPS. Furthermore, technical aspects of ALPPS and whether ALPPS was used in a liver-first approach did not affect CSS. The equal oncological outcome of liver- and primary-first approach in our study has been also reported by other studies in a non-ALPPS setting.[31,32] However, the occurrence of severe postoperative complications after ALPPS resulted in inferior long-term survival. This fact underlines the importance of an uneventful postoperative course for favorable oncological outcome. Although not assessed in the present study, postoperative complications might delay or even prevent the start of adjuvant or additive chemotherapy after ALPPS. This assumption is supported by a previous study where a short chemotherapy-free interval of less than or equal 10 weeks was associated with superior survival after ALPPS.[33]

lthough histological margin status is considered as oncologic standard assessment after resection of CRLM, there is growing literature challenging the prognostic significance of R0/1 resection in the modern era of multimodal liver tumor treatment.[34–36] Furthermore, ''disappearing'' or ''ablated'' lesions are not amenable to histological margin assessment. Considering that a significant proportion of ALPPS patients underwent additional ablation procedures or might have disappearing lesions after effective response to chemotherapy, histological margin assessment is not applicable to these case scenarios. For all of these reasons, we did not include margin status in our analytical statistics.

Another important finding of the study was that hepatic recurrence after ALPPS was a frequent event especially during the first 2 years after liver surgery. The hepatic recurrence rate of 60% in the present study compares to analogous figures reported for previous ALPPS[37] and conventional TSH series.[17] Despite the observed high recurrence rate, many patients achieved remarkable long-term survival especially those in whom treatment of hepatic recurrence included repeat liver surgery and/or ablation (Fig. 3B). The benefit of repeat liver surgery has been repeatedly demonstrated for recurrent CRLM after initial one- and two-stage hepatectomy.[38–41] In our study, repeat liver surgery and/or ablation for recurrent CRLM after ALPPS was associated with superior survival compared to those without intervention and treated by chemotherapy. However, this observation needs to be interpreted with caution since patients with recurrent disease amenable for local treatment (resection and/or ablation) might present a selected group compared to those with diffuse tumor spread who can undergo chemotherapy only. The fact that the local treatment group had a more favorable tumor biology with fewer *K/N-RAS* mutations and right-sided colon tumors suggest the assumption of a selection effect. We would contend, however, that patients with hepatic recurrence after ALPPS responding to chemotherapy should be always evaluated for repeat liver resection or ablation.

The strength of this study relates to the large multicenter study population of more than 500 ALPPS patients with actual follow-up of all participating centers. In addition, the long median follow-up time of more than 3 years facilitated to draw meaningful long-term oncological conclusions for this special cohort. The complementary collection of tumor-related variables beyond those captured in the registry such as *K/N-RAS* status and the presence of concomitant lung metastases further increased the quality of the oncological outcome analysis. The study was also associated with limitations, which were

mainly related to the retrospective study design and incomplete data for certain variables. Missing data were either not identified in the medical records or literally not available in case of not performed tests such as serum CEA measurements or *K/N-RAS* analysis.

In conclusion, this large cohort provides the first and convincing evidence that patients with primarily unresectable CRLM treated by ALPPS have not only low perioperative mortality, but achieve appealing long-term oncologic outcome especially those with favorable tumor biology and good response to chemotherapy. This data should have a key impact in offering ALPPS to this population of patients.

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