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Role of Neoadjuvant Chemotherapy in Resectable Synchronous Colorectal Liver Metastasis; an International Multi-Center Data Analysis Using Livermetsurvey

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Background and objectives: The use of neo-adjuvant chemotherapy in resectable synchronous liver metastasis is ill defined. The aim of this study was to evaluate neo-adjuvant chemotherapy on outcomes following liver resection for synchronous CLM.
Methods: An analysis of a multi-centric cohort from the LiverMetSurvey International Registry, who had undergone curative resections for synchronous CLM was undertaken. Patients who received neo-adjuvant chemotherapy prior to liver surgery (group NAS; n = 693) were compared with those treated by surgery alone (group SG; n = 608). Baseline clinicopathological variables were compared. Predictors of overall (OS) and disease free survival (DFS) were subsequently identified.
Results: Clinicopathological comparison of the groups revealed a greater proportion of solitary metastasis in the SG compared to the NAS group (58.8% versus 38.4%; $P < 0.001$) therefore a separate analysis of solitary versus multi-centric analysis was performed. N-stage (>N1), number of metastasis (>3), serum CEA (>5ng/ml) and no adjuvant chemotherapy independently predicted poorer OS, while N-stage (>N1), serum CEA (>5ng/ml) and no adjuvant chemotherapy independently predicted poorer DFS. Neo-adjuvant chemotherapy did not independently affect outcome.
Conclusion: We present an analysis of a large multi-center series of the role of neo-adjuvant chemotherapy in resectable CLM and demonstrate no survival advantage in this setting.
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KEY WORDS: **neo-adjuvant; chemotherapy; synchronous; liver metastasis; liver surgery**

INTRODUCTION

Hepatic resection has long been the mainstay treatment for colorectal liver metastasis (CLM) with 5-year survival following resection with curative intent approaching 45–60% [1–4]. However, recurrent disease remains common with disease free survival rates of 25–30% [3]. Therefore, while the overall survival remains encouraging, the disappointing recurrence rate, and poor long-term survival have resulted in much interest in chemotherapy as an adjunct to the management of such patients. In unresectable CLMs, the use of neo-adjuvant chemotherapy, in a bid to improve resectability rates, is well documented and predictors of such response have been analyzed [5,6]. However, in initially resectable disease the benefit of neo-adjuvant treatment is less clear.

To-date, the EORTC Intergroup trial 40,983 remains the largest prospective randomized-controlled trial analyzing the role of neo-adjuvant chemotherapy in resectable CLMs [7]. In this trial, patients with resectable disease were randomized to receive surgery alone versus surgery with neo-adjuvant and adjuvant chemotherapy. The trial showed an improved disease free survival in patients receiving chemotherapy but failed to demonstrate the optimal sequence for the administration of such treatment and groups that may specifically benefit from targeted chemotherapy. Furthermore, nearly two thirds of

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patients recruited in this study had metachronous disease; representing a mixed biology of disease.

Specifically analyzing the role of neo-adjuvant chemotherapy in metachronous liver metastasis, Adam et al. showed no benefit of this treatment in solitary CLMs [8]. By interrogating a prospective multi-center European database (LiverMetSurvey; http://www.livermetsurvey.org) the authors also showed a benefit of post-operative chemotherapy in solitary metachronous CLMs exceeding 5 cm in diameter. However, synchronous CLMs, represent a different tumor biology and the role of neo-adjuvant chemotherapy in resectable synchronous CLMs remains unclear.

Using the prospective database of the LiverMetSurvey, we aimed to analyze the role of neo-adjuvant chemotherapy in synchronous resectable liver only colorectal metastasis.

METHODS

A retrospective analysis of a prospectively held European multi-center database of a cohort of patients who have undergone liver resections for only colorectal metastasis over a 11 years period was undertaken (May 2000–June 2011) in the LiverMetSurvey International Registry. Specifically, data were trawled and extracted for liver resections for synchronous, resectable, liver only metastasis.

The LiverMetSurvey is an international database of patients with Metastatic colorectal cancer that consists of data voluntarily registered by 250 centers in 52 countries. Data are categorized into patient demographics, the primary tumor, secondary tumor details, extent of surgical resection, post-operative complications, details of chemotherapy (neo-adjuvant and adjuvant), time and nature of recurrence, and survival using a standardized online questionnaire.

Definitions

Eligibility criteria for inclusion in this study were as follows:

- Resectability, pathological data, chemotherapy regimens, and follow-up data available
- Radiological and pathological confirmed liver metastasis
- Synchronous liver metastasis (defined as resection within 6 months before or after surgery for primary tumor)
- Primary tumor resectable
- Secondary tumor/tumors resectable at presentation without neo-adjuvant chemotherapy and performed with no remnant disease. This was in order to analyze resections performed for metastasis that were resectable prior to presentation (without chemotherapy) and resected with macroscopic clearance of disease
- No detectable extrahepatic disease at presentation
- For the patients receiving neo-adjuvant chemotherapy, at least three cycles administered
- At least 2 months follow-up

Study Design

Two groups were compared; those patients who had surgery upfront and those who received at least three cycles of optimal neo-adjuvant combination chemotherapy before liver resection. Chemotherapy agents used consisted of regimes containing 5-fluorouracil (5-FU), leucovorin, and oxaliplatin or 5-FU, leucovorin, and irinotecan with or without bevacizumab or cetuximab. Patients receiving 5-FU alone were excluded from the study.

Using the eligibility criteria as described above, patients included in the analysis with resectable, liver only colorectal metastasis who received at least 3 doses of optimal neo-adjuvant chemotherapy followed by surgery (NAS group) or underwent surgery upfront (SG group).

For the first stage of the analysis a comparative analysis of the demographic and clinico-pathological characteristics of the NAS and SG group was performed in order to analyze the differences between the 2 studied populations. Following this, the overall and disease free survival (OS and DFS respectively) of the entire cohort as well as its independent predictors was analyzed. By performing the first stage analysis, we identified a significantly greater proportion of patients in the NAS group with multi-centric tumors. As there were significantly more patients with multi-centric tumors in the NAS groups (See Table I), we performed a subcohort analysis on solitary and multi-centric tumors as well as the influence of chemotherapy on survival.

Statistical Analysis

Categorical variables were compared by χ^2 analysis and continuous variable that were parametric and non-parametric distributed were compared by *t*-test and Mann-Whitney U test, respectively. Survival analysis was performed by Kaplan-Meier method and compared by log-rank. Multi-variate analysis was performed by Cox proportional hazards. A significance value of $P < 0.05$ was used. For multi-variable analysis, significant factors on univariate analysis were included in the multi-variate model. All statistical analysis was performed on SPSS version 19 (SPSS Institute, Cal, USA).

RESULTS

A total of 11,001 patients underwent liver resection for CRLM in the study period (May 2000–June 2011). A total of 5,589 patients had synchronous liver metastasis. Of these 1,613 had disease that was unresectable or of uncertain resectability at presentation, 793 had non-curative resections (non-curative hepatectomy n = 338, hepatectomy with metastatic disease n = 356, hepatectomy not performed n = 14, and extrahepatic disease at time of liver resection n = 85), 59 patients received neo-adjuvant chemotherapy but less then three cycles with 1,095 patients having missing neo-adjuvant chemotherapy details, 229 patients had incomplete pathological data, 210 less then 2 month follow-up and 289 patients had incomplete follow-up . Therefore, 1,301 patients met the inclusion criteria for synchronous resectable liver only colorectal metastasis with 693 and 608 patients in the NAS and SG groups respectively (Fig. 1).

Clinico-Pathological Variables Between S and NAS groups

There was a difference in age distribution between the two groups with the proportion of patients younger than 60 receiving neo-adjuvant chemotherapy being significantly greater (67.7% versus 61.0% for the NAS and SG group respectively; $P = 0.02$). With

TABLE I. Comparison of Clinico-Pathological Data of the NAS (n = 693) and SG Groups (n = 608)

Variable	Group NAS (%)	Group SG (%)	*P*-value
Age > 60	61.0	67.7	0.02
Sex (male)	60.3	60.9	0.84
Primary pathology			
>T2	91.5	92.3	0.61
>N1	28.3	30.8	0.33
Secondary pathology			
Size of mets > 5cm	15.8	14.1	0.41
Solitary met	38.4	58.8	<0.001
Post operative chemotherapy	68	68	0.98

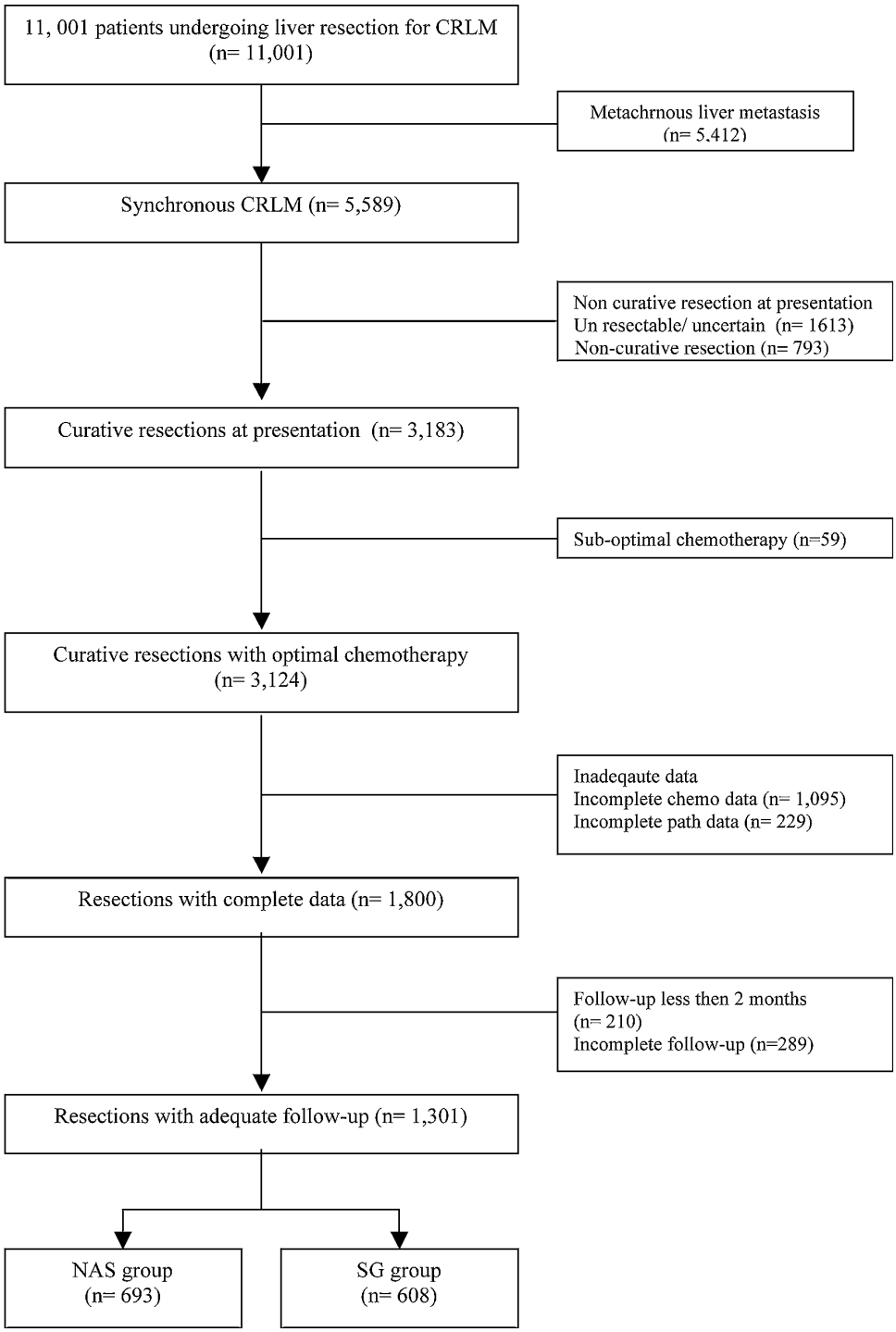


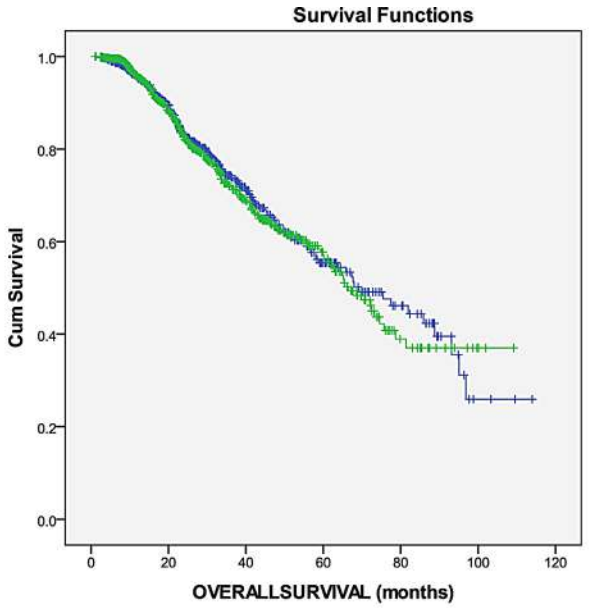
Fig. 1. Flowdiagram of data reduction prior to final analysis.

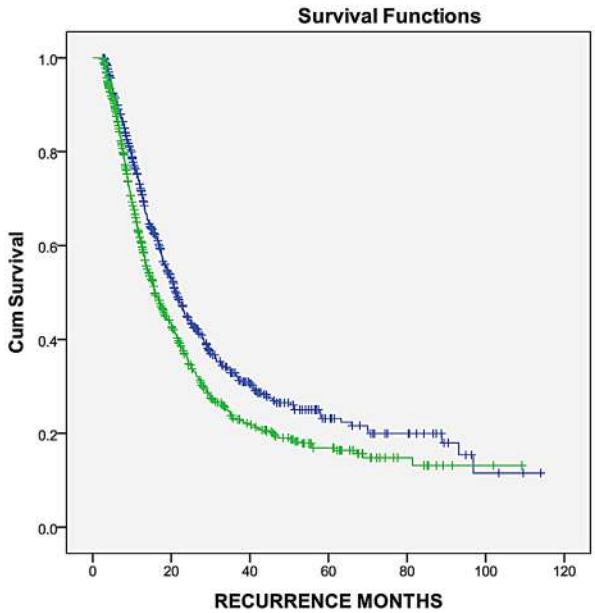
regard to the primary pathology, there was no significant difference between the proportion of patients with greater than T2 and N1 disease, respectively (Table I). In the NAS group, 503 patients received Oxaliplatin and 190 received Irinotecan based chemotherapy. Second line chemotherapy with bevacizumab ($n = 100$), cetuximab ($n = 30$), and capecitabine ($n = 100$) was also used in this group. Further, the proportion of patients with metastasis greater than 5 cm in size, in both groups, was not significantly different. However a smaller proportion of patients in the NAS group had solitary tumors (58.8% versus 38.4% in the SG and NAS groups respectively; $P < 0.001$). As the proportion of patients with multi-centric tumors was greater in the NAS group, which indeed may affect survival analysis, a separate analysis of solitary versus multi-centric resections were undertaken.

Overall and Disease-Free Survival of NAS and S Patient Cohort

With a median follow-up of 31 months (2–114 months), the overall 1-year and 3-years survival was 95% and 73%, respectively; and the disease free survival was 67% and 28%, respectively for the entire cohort. The overall rate of recurrence in NAS and SG group was 65% and 60%, respectively. The pattern of recurrence (intra-hepatic, extra-hepatic, or both) at time of presentation with recurrent disease was similar in both the NAS and SG group (Fig. 2) illustrating that neo-adjuvant chemotherapy had no effect on the site of recurrent disease. This distribution was not statistically significant ($P = 0.17$).

The overall survival at 1-year and 3-years for the SG and NAS groups, respectively, was 95% and 74% versus 95% and 72%,





	12-months	24-months	36-months	48-months
Numbers at risk (NAS)	520	338	214	138
Numbers at risk (SG)	484	314	193	119

Fig. 2. Overall survival (above) and Disease free survival (below) of entire cohort for NAS (green) and SG (blue) with associated numbers at risk.

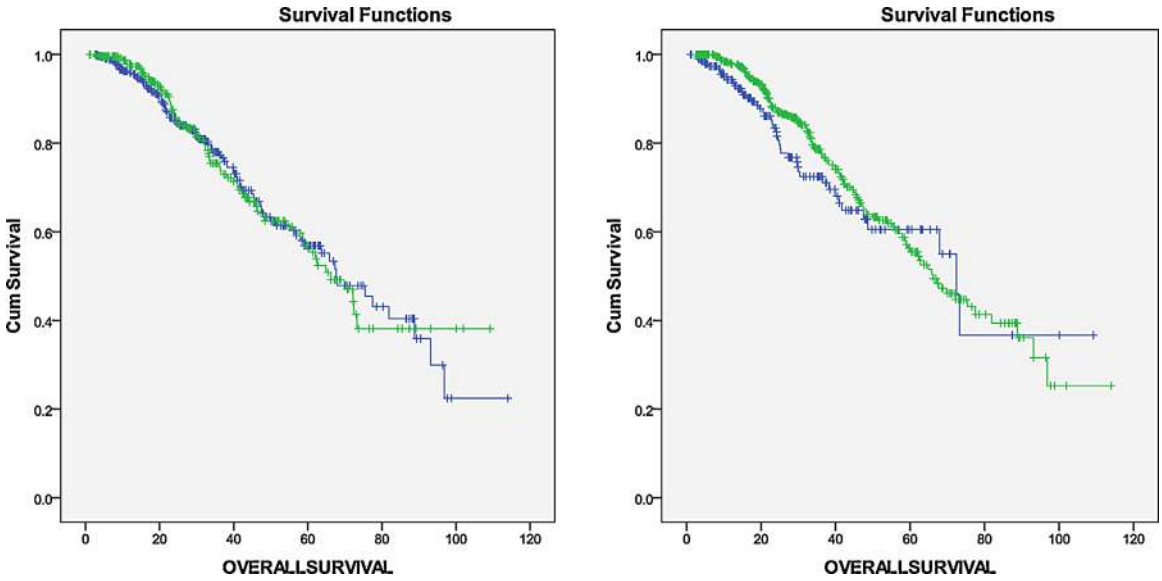


Fig. 3. Overall survival patients in the NAS (green) versus SG (blue) [LEFT] and receiving post-operative chemotherapy (green) versus no post-operative chemotherapy (blue) [RIGHT] with solitary liver metastasis.

respectively ($P = 0.72$) (Fig. 3). On univariate analysis, the overall survival was negatively influenced by N-stage greater the N1 ($P < 0.001$), more than three metastasis ($P = 0.002$) and CEA greater than 5 ng/ml ($P = 0.03$), no post-operative chemotherapy (Table II). On multi-variate analysis, N-stage greater than N1, CEA greater than 5 ng/ml, and no post-operative chemotherapy independently predicted poorer overall survival (Table III).

TABLE II. Univariate Predictors of OS and DFS for Study Cohort (n = 1,301)

	Overall survival			Disease free survival		
Variable	1-year	3-years	*P*-value	1-year	3-years	*P*-value
Age						
<60	96	72	0.51	66	24	0.29
≥60	95	74		67	24	
Location						
Colon	95	75	0.34	67	28	0.44
Rectum	96	68		66	26	
T-stage						
≤T2	97	75	0.40	67	30	0.74
>T2	95	73		67	28	
N-stage						
≤N1	97	76	<0.001	70	31	<0.001
>N1	92	62		60	19	
No of mets						
Solitary	97	77	0.25	70	32	0.001
Multi-centric	94	70		64	24	
Multi mets						
≤3	96	75	0.02	68	29	0.001
>3	92	54		60	22	
Size						
≤5cm	96	74	0.10	68	28	0.34
>5 cm	92	70		62	28	
CEA						
≤5	97	82	0.03	75	41	<0.001
>5	95	67		66	25	
Neoadj chemo						
Yes	95	72	0.72	62	23	<0.001
No	96	74		73	33	
Post-operative chemotherapy						
Yes	97	76	0.005	71	29	0.002
No	92	67		58	26	

The disease free survival at 1-year and 3-years for the SG and NAS groups, respectively, was 73% and 33% versus 62% and 23%, respectively ($P < 0.001$); a poorer DFS in the NAS group (Fig. 3) with a median time to recurrence in the NAS and SG group being 14 and 17 months, respectively. On univariate analysis, N-stage greater than N1 ($P < 0.001$), multi-centric tumors ($P = 0.001$), greater than three metastasis ($P = 0.001$), CEA greater than 5 ng/ml ($P < 0.001$), neo-adjuvant chemotherapy ($P < 0.001$) and no post-operative chemotherapy ($P = 0.002$) negatively influenced disease free survival (Table II). On multi-variate analysis, N-stage greater than N1, CEA > 5ng/ml and no post-operative chemotherapy independently predicted disease recurrence (Table III). Of note, neo-adjuvant chemotherapy did not independently predict DFS for the entire cohort.

Solitary (n = 612) Versus Multi-Centric (n = 689)

There were a significantly greater proportion of patients with multi-centric tumors in the NAS group. Hence, the survival analysis of the two groups may be influenced by this factor. For this reason, we studied the influence of neo-adjuvant chemotherapy on survival in patients with solitary and multi-centric tumors separately.

In patients with solitary liver metastasis there was no difference in overall survival in patients who have received preoperative neo-

TABLE III. Independent (Multi-Variate Analysis) Predictors of OS and DFS

Factors and groups	P	RR	95% CI
Overall survival			
N-stage > N1	0.009	1.45	1.09–1.91
CEA > 5	0.01	1.44	1.07–1.92
Post-op chemo	0.04	1.35	1.01–1.80
Disease free survival			
N stage > N1	0.01	1.41	1.07–1.87
CEA > 5	0.01	1.46	1.10–1.95
Post-op chemo	0.05	1.33	1.00–1.78

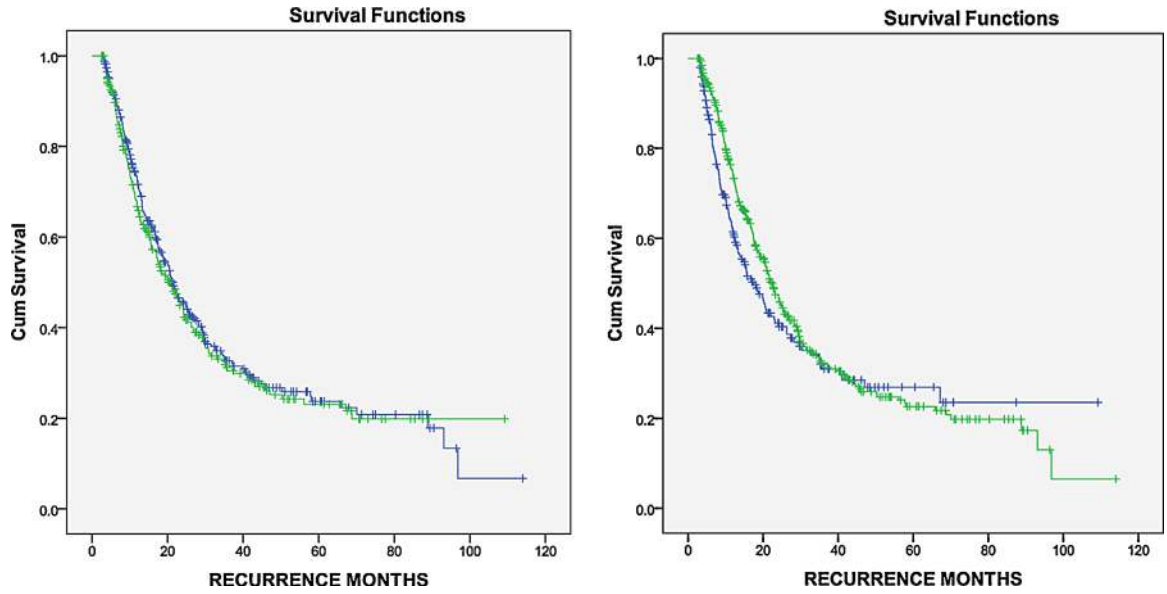


Fig. 4. Disease free survival patients in the NAS (green) versus SG (blue) [LEFT] and receiving post-operative chemotherapy (green) versus no post-operative chemotherapy (blue) [RIGHT] with solitary liver metastasis.

adjuvant chemotherapy and those that did not with 1-year/3-years OS being 98%/75% and 96%/78% ($P = 0.95$), respectively (Fig. 4). Equally there was no significant difference in OS of patients with solitary metastasis receiving post-operative chemotherapy (Fig. 4; $P = 0.38$). With respect to disease free survival, there was no significant difference in survival at 1-year/3-years of patients in the NAS and SG groups being 67%/31% and 72%/32%, respectively (Fig. 5; $P = 0.57$). Post-operative chemotherapy resulted in no significant difference in DFS of patients with solitary liver metastasis (Fig. 5; $P = 0.18$)

In patients with multi-centric liver metastasis there was no difference in overall survival in patients who had received neo-adjuvant chemotherapy and those that did not with 1-year/3-years OS being 94%/71% and 95%/67% (Fig. 6; $P = 0.86$), respectively. Patients with multi-centric tumors receiving post-operative chemotherapy had a significantly better overall survival when compared to those that did not with 1-year/3-years survival being 96%/73% and 90%/63%, respectively (Fig. 6; $P = 0.01$). With respect to disease free survival, there was significantly poorer survival in the NAS group compared to the SG group with a 1-year/3-years survival of 58%/18% and 73%/33%, respectively (Fig. 7; $P < 0.001$). There was a better DFS in patients receiving post-operative chemo compared to those that did not with 1-year/3-years survival being 68%/25% and 54%/21% of patients (Fig. 6; $P = 0.007$).

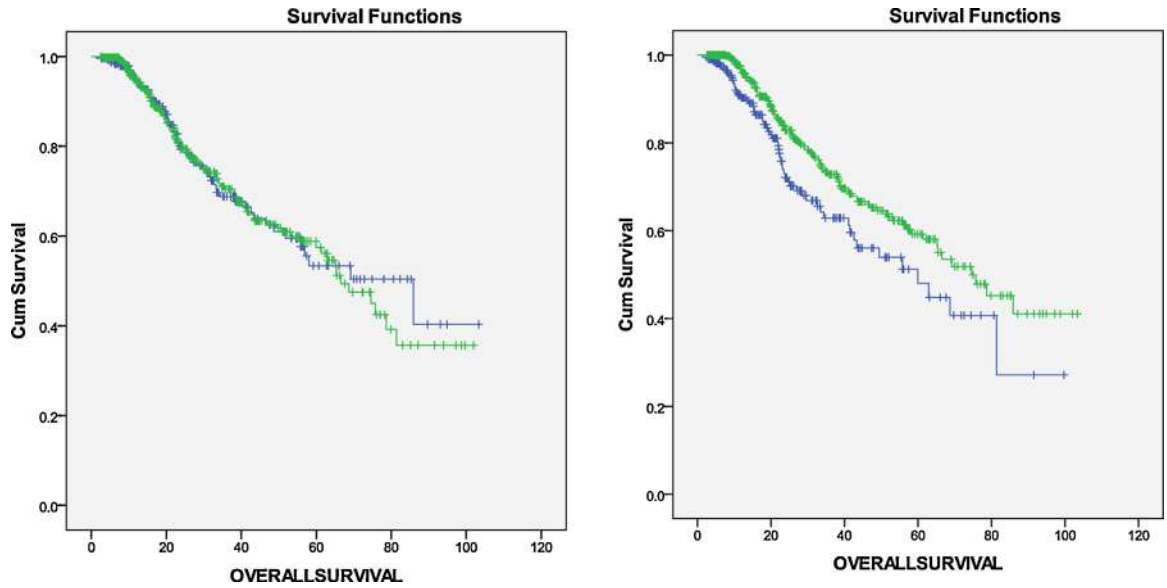


Fig. 5. Overall survival patients in the NAS (green) versus SG (blue) [LEFT] and receiving post-operative chemotherapy (green) versus no post-operative chemotherapy (blue) [RIGHT] with multicentric liver metastasis.

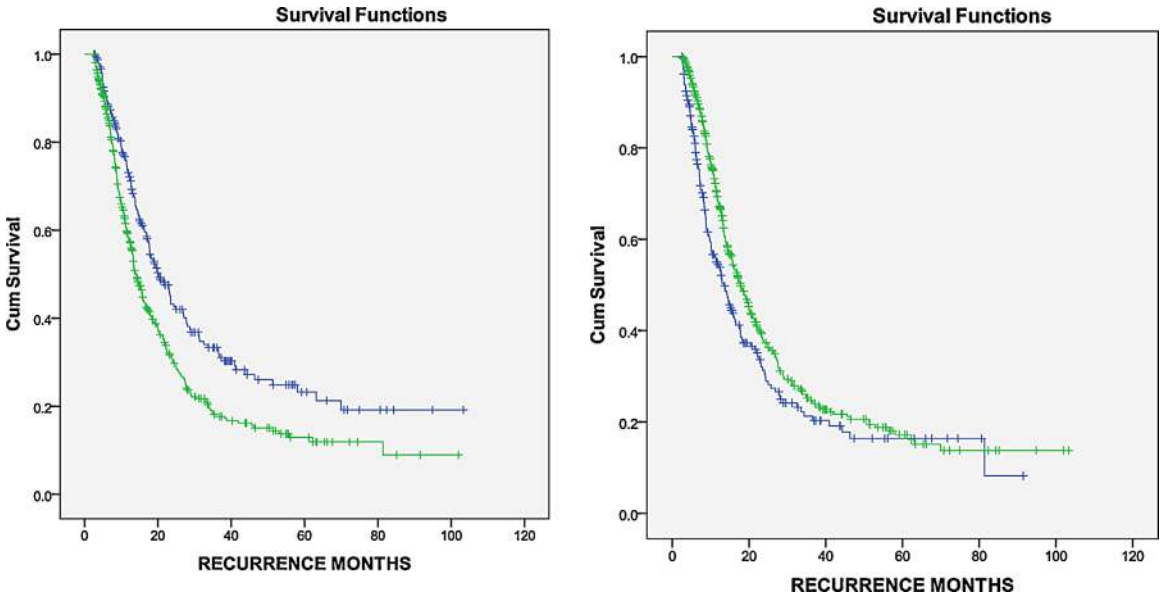


Fig. 6. Disease free survival patients in the NAS (green) versus SG (blue) [LEFT] and receiving post-operative chemotherapy (green) versus no post-operative chemotherapy (blue) [RIGHT] with multicentric liver metastasis.

DISCUSSION

Liver resections have become the mainstay in treatment of colorectal liver metastasis. However, the relatively high recurrent rates and low "true" curative resections have led to the development of chemotherapy strategies as an adjunct to treatment in such resections. A recent review of 23 studies in over 3,000 patients showed a benefit from neo-adjuvant chemotherapy [9]. However, this study depicted the heterogeneity of published retrospective series that analyze outcomes in patients of different burden of disease receiving combinations of neo-adjuvant and adjuvant chemotherapy; rarely analyzing specific disease cohorts and intent of treatment. Specifically, looking at the role of neo-adjuvant chemotherapy, a few retrospective studies have analyzed its role albeit in small series and not specifically in synchronous disease [10–12].

By using an international prospectively held international registry (LiverMetSurvey), we analyze here the role of neo-adjuvant chemotherapy specifically in patients undergoing curative resections for colorectal liver [only] metastases. A strict inclusion criteria were employed for the study cohort resulting in a significant data reduction from 11,001 to 1,301 patients. Previous similar studies have

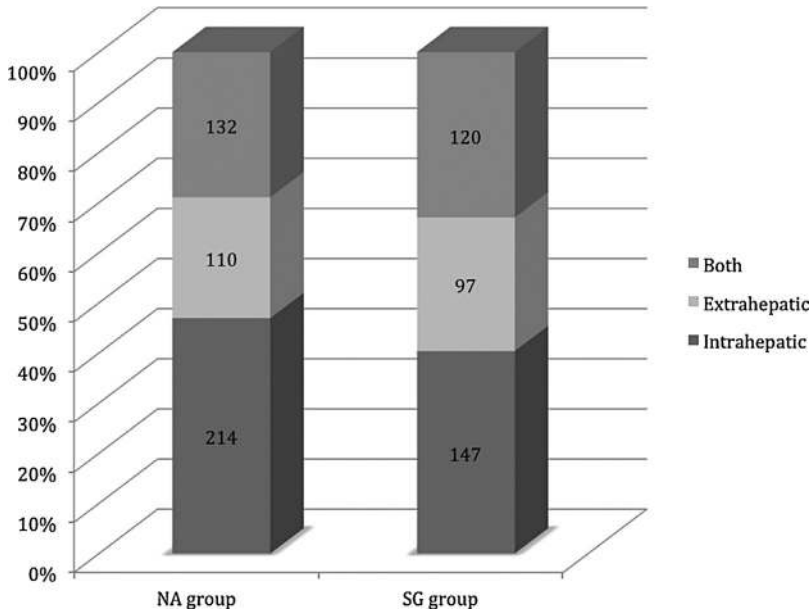


Fig. 7. Percentage stack columns (with absolute numbers in figures) of site or recurrent disease at first presentation of disease recurrence ($p = 0.17$).

included patients with extrahepatic disease [11,12], metachronous disease [7,11,13], and due to the retrospective nature of the analysis the curative intent of neo-adjuvant chemotherapy and surgery were unclear. Having used stringent inclusion criteria the patients were split into 2 groups; 693 and 608 patients in the NAS and SG groups, respectively, the largest retrospective analysis to-date.

Firstly looking at overall survival, we found no difference in patient in the NAS and SG groups. Instead, in multi-variate analysis found that N-stage (greater than N1), greater than three metastasis, CEA $>$ 5ng/ml, and no post-operative chemotherapy, independently effected overall survival. Though the initial published results of the EORTC Intergroup trial showed a worse overall survival in patients not receiving chemotherapy, the study included patients with metachronous metastasis and the surgery alone group did not receive post-operative chemo. Specifically looking at the role of neo-adjuvant treatment, Hewes et al. showed similar outcome demonstrated here, with a worse overall survival in the neo-adjuvant group [13]. More recently, a study by Reddy et al. analyzing this treatment in resectable synchronous metastasis also demonstrated a worse overall survival in patients receiving pre-hepatectomy chemotherapy [12]. However, it is noteworthy that the group receiving pre-hepatectomy chemotherapy had a significantly worse N-stage, larger diameter tumors, and a greater number of metastasis making the interpretation of these results difficult and the expected poorer survival in this group with no obvious advantage to pre-hepatectomy chemotherapy. A raised CEA level independently predicting poorer outcome following liver resection, as demonstrated here, has been shown in a number of different studies [14,15]. Put together, an N-stage greater than N1, number of metastasis $>$ 3 and a raised CEA level reflects bad disease burden and in synchronous resectable disease, at present, neo-adjuvant chemotherapy has a limited effect on improving overall survival.

Secondly, looking at disease free survival, once again we have found a worse survival in patients with N-stage greater than N1, a raised CEA level, and lack of post-operative chemotherapy. However, here we also found a trend toward worse DFS associated with patients given neo-adjuvant chemotherapy (Fig. 3) though it was not an independent predictor of disease free survival (Table III) . This may be explained in two ways. First, that the neo-adjuvant chemotherapy had no effect on tumor biology and therefore delaying the operative intervention by administration of treatment resulted in disease progression; macroscopic or microscopic. This issue of tumor progression while on chemotherapy will be discussed later. Second, as seen in other studies, the cohort receiving neo-adjuvant therapy may indeed have had a worse disease burden. This indeed was the case, with more patients in the NAS group having multi-centric tumors but patients were well matched for T-stage, N-stage, size of metastasis, and administration of post-operative chemotherapy. Therefore, a separate analysis of solitary versus multi-centric tumors was undertaken and discussed below. While the high recurrence rate associated with liver resections for colorectal metastasis remains disappointing, the factors identified that affect this rate are similar to those affecting overall survival and in turn are not improved by administration of neo-adjuvant chemotherapy in synchronous metastasis.

When analyzed, there was no effect on OS and DFS solitary synchronous liver metastasis receiving neo-adjuvant or post-operative chemotherapy. In a study by Adam et al. on solitary metachronous metastasis, the authors also demonstrated no influence of neo-adjuvant chemotherapy on survival but an improved survival with post-operative chemotherapy [8]. In contrast, for multi-centric disease, while neo-adjuvant chemotherapy resulted in a poorer DFS, post-operative chemotherapy conferred a better OS and DFS. Putting together, this data suggest that in solitary and multi-centric synchronous metastasis, neo-adjuvant chemotherapy confers little improvement on survival, but post-operative chemotherapy is beneficial.

Though this remains the largest analysis of the role of neo-adjuvant chemotherapy in resectable synchronous colorectal liver metastasis, a limitation of this study lies in its retrospective nature. By interrogating a prospectively held multi-Centre database, the trends in survival following liver resections with or without chemotherapy are not worthy, however, the decisions to administer chemotherapy, be it pre- or post-operatively in this cohort are not clearly detailed. These decisions made on a case by case basis by numerous participating centers, would mean that the influence of combinations of bad prognostic indicators and then the administration of chemotherapy may influence the overall result. The only method by which these factors can be removed is by a well designed prospective multi-center randomized controlled trial. In the absence of such a study, the influence of neo-adjuvant chemotherapy in this large cohort is still not worthy.

The principles behind neo-adjuvant chemotherapy in the setting of resectable synchronous colorectal liver metastasis are that (1) the advantage conferred by neo-adjuvant chemotherapy is greater then morbidity and risk associated with its administration prior to resection, (2) progression on neo-adjuvant chemotherapy represents poor disease biology and therefore precludes unnecessary resections, (3) a response to chemotherapy might guide the administration of post-operative chemotherapy and (4) synchronous liver metastases represent systemic spread of malignancy and may require systemic treatment as an adjunct to surgery in order to improve survival. These four points will now be discussed.

Neo-adjuvant chemotherapy is associated with significant morbidity in itself as well as resultant increased morbidity in the subsequent liver operation; depending on the intensity of the regime and period of recovery prior to surgery [7]. The effect on the macroscopic and microscopic constituents of the liver has been described [16,17]. The EORTC study demonstrated significantly worse complications, though minor and transient, following liver surgery of patients in the chemotherapy group.) However, liver resections were performed 2–5 weeks following resection. It is currently widely accepted that liver resection is usually undertaken after 4 weeks following neo-adjuvant chemotherapy and may in part explain the higher morbidity in the chemotherapy group in this early study when compared to fairly low rates in more recent publications [12,13]. Therefore, with regard to this first point, the improvements in operative techniques coupled with understanding of the effects on the liver of chemotherapy have resulted in low morbidity rates.

With regard to the second point, the response to chemotherapy being surrogate marker of disease was shown by Adam et al. where tumor progression while on chemotherapy (seen in a quarter of patients), with the 5 year survival in patients with greater than 3 metastasis being as low as 8% [18]. In a larger series, Neumann et al. found that non response to chemotherapy did not independently predict survival [19]. Finally in a recent analysis of LiverMetSurvey on over 2,000 liver resections, progressive disease was found in 8% on chemotherapy and though this negatively affected survival, in the absence of other negative factors, this was not a contraindication to resection [20]. The response of chemotherapy was not analyzed here, having previously been evaluated in the same database. Specifically, resectable disease undergoing surgery with curative intent (as analyzed in the present study) coupled with the data shown here, and in other studies, that the effect of neo-adjuvant chemotherapy is limited, this test of biology while theoretically useful may have limited effect on survival in this cohort.

With regard to the fourth point above, intuitively, synchronous metastasis represents systemic disease and will require systemic treatment to improve survival. The question remains is this beneficial in the neo-adjuvant or adjuvant setting or both? The large European multi-center series analyzed here have demonstrated that, synchronous resectable liver metastasis represents bad tumor biology and in this setting the effect of neo-adjuvant chemotherapy is limited. Post-operative chemotherapy improves overall and disease free survival particularly in multi-centric disease.

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