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ORIGINAL ARTICLE

Outcomes of liver-first strategy and classical strategy for synchronous colorectal liver metastases in Sweden

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Abstract

Background: Patients with synchronous colorectal liver metastases (sCRLM) are increasingly operated with liver resection before resection of the primary cancer. The aim of this study was to compare outcomes in patients following the liver-first strategy and the classical strategy (resection of the bowel first) using prospectively registered data from two nationwide registries.

Methods: Clinical, pathological and survival outcomes were compared between the liver-first strategy and the classical strategy (2008–2015). Overall survival was calculated.

Results: A total of 623 patients were identified, of which 246 were treated with the liver-first strategy and 377 with the classical strategy. The median follow-up was 40 months. Patients chosen for the classical strategy more often had T4 primary tumours (23% vs 14%, P = 0.012) and node-positive primaries (70 vs 61%, P = 0.015). The liver-first patients had a higher liver tumour burden score (4.1 (2.5–6.3) vs 3.6 (2.2–5.1), P = 0.003). No difference was seen in five-year overall survival between the groups (54% vs 49%, P = 0.344). A majority (59%) of patients with rectal cancer were treated with the liver-first strategy.

Conclusion: The liver-first strategy is currently the dominant strategy for sCRLM in patients with rectal cancer in Sweden. No difference in overall survival was noted between strategies.

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Introduction

Colorectal cancer is the third most common malignancy in the world[1,2] and 15–20 per cent of patients present with synchronous liver metastases at diagnosis.[3–5] Surgical resection of all tumours, when feasible, currently offers the only potential for cure. Traditionally, the primary tumour is resected as the first intervention, followed by resection of the liver metastasis in a second stage; this is called the classical strategy. In the last decade, increased focus has been on preoperative chemotherapy and resection of the liver metastases as the first intervention, followed by resection of the primary tumour, here described as the liver-first strategy, as introduced by Mentha *et al.*[6]

The liver-first strategy potentially avoids the disadvantage of the classical strategy, especially in the case of complications after bowel surgery, of postponing liver resection and the risk of progression of the liver disease beyond resectability. In addition, in the case of pre-treatment of rectal primaries with long course chemo-radiation, liver resection can be performed in the waiting time between radiation and rectal resection, possibly shortening the total treatment time. No survival differences have been

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demonstrated between the different strategies, although no randomized trials have been conducted on the subject.[7–10] The liver-first strategy appears safe for selected patients.

Previous studies are limited to single centre retrospective studies or include a relatively small number of patients.[11] The indications for proposing the liver-first strategy to patients are still evolving. No nationwide study on the liver-first strategy has previously been published. The aim of the present study was to compare the liver-first with the classical strategy for patients presenting with synchronous colorectal liver metastases (sCRLM), focussing on patient selection and survival, based on data from quality assurance registries in Sweden.

Methods

Patients were identified at the time of entry from the Swedish Colorectal Cancer registry (SCRCR) and the National Quality Registry for liver and biliary cancer (SweLiv) from January 2008 to December 2014. In the SCRCR, all patients diagnosed with adenocarcinoma of the colon or rectum are registered. In the SweLiv all patients who develop primary malignancy of the liver, gallbladder or bile ducts and all interventions related to both primary and secondary malignancy of the liver are registered. The SCRCR was launched in 2007 while the SweLiv was launched in 2008, and the registration of data is prospective. The SCRCR has been described previously[12] and covered 94–98% of all colorectal cancers during the study period, while SweLiv covered more than 90% of all primary liver and bile duct cancers.[13]

From the databases, patients with metastatic colorectal cancer at initial staging (before any resection) were identified and defined as having synchronous liver metastases. Patients who had undergone acute bowel resection or synchronous bowel and liver resections were excluded. The subset of patients who had undergone both bowel and liver resection within 12 months constitutes the study patient cohort. Patients with sCRLM who had only undergone liver resection but no bowel resection were identified separately. Patients were stratified according to the localization of the primary tumour (colon vs. rectum). A comparison was made between patients operated with the liver-first and the classical strategies. A major liver resection was defined as a resection of $\geq$3 Couinaud's segments. An R0 resection was defined as microscopically tumour free resection margin. A liver tumour burden score (TBS) was calculated for each patient [TBS^2 = (maximum tumour diameter in centimetres)^2 + (number of liver lesions)^2].[14]

Statistics

Summary statistics are presented as whole numbers and percentages for categorical variables, or as medians with interquartile ranges (IQRs) for continuous variables. A Mann–Whitney U-test was used to compare continuous data and Fischer's exact test was used for categorical data. Kaplan Meier analysis was used to estimate survival from the time of diagnosis. Overall survival was calculated from the time of diagnosis. To analyse the effect of patient and tumour specifics on survival, multi- and univariate Cox proportional hazards (PH) models were used for independent variables. A P-value less than 0.05 was considered statistically significant. Statistical analysis was performed using R (R Core Team (2016). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/).

Results

A total of 707 patients with sCRLM who underwent liver resection were identified. Eighty-four patients with metastatic colorectal cancer underwent liver resection but no bowel resection. A total of 623 patients underwent both bowel and liver resections within 12 months, of which 246 (39%) underwent a liver-first strategy and 377 (61%) underwent a classical strategy. The characteristics of the patients in the classical and liver-first groups are shown in Table 1. Two patients died (0.5 per cent) within 30 days after liver resection in the classical strategy group. In the liver-first group, none died within 30 days after bowel resection.

A total of 317 (50%) patients received preoperative chemotherapy before the first resection. The use of preoperative chemotherapy in the different groups is shown in Table 1.

Table 1 Characteristics of resected patients

	Classical strategy	Liver-first strategy	P‡
Number of patients	377	246	
Gender (Male)	234 (62)	161 (65)	0.397
Age (years)*	66 (58–73)	62 (54–69)	<0.001§
ASA score 3–4	74 (20)	57 (23)	0.365
BMI (kg/m^2)*	25 (23–28)	25 (23–27)	0.127§
Primary rectal cancer	115 (31)	166 (67)	<0.001
Chemotherapy before first resection	97 (26)	220 (92)	<0.001
Radiotherapy before bowel resection	84 (22)	153 (62)	<0.001
T4 primary tumour	85 (23)	35 (14)	0.012
Lymph node positive primary tumour	264 (70)	149 (61)	0.015
R0 primary tumour resection	344 (92)	221 (91)	0.663
Liver TBS*	3.6 (2.2–5.1)	4.1 (2.5–6.3)	0.003§
Major liver resection	152 (41)	125 (52)	0.008
R0 liver resection	262 (86)	173 (86)	0.896

Values in parentheses are percentages unless indicated otherwise: *values are median (interquartile range). ASA, American Society of Anesthesiologists; BMI, body mass index; R0, radical resection; TBS, tumour burden score. ‡Fischer's exact test, except §Mann–Whitney U test.

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The median follow-up time was 40 (27–57) months. No difference in overall survival was found (P = 0.344), with an overall five-year survival of 54% for the classical group and 49% for the liver-first group. A total of 264 patients had died at the end of the study of the 623 patients that underwent both bowel and liver surgery. Kaplan Meier survival curves for resected patients are shown in Fig. 1. The time from the first to the second operation was 4.7 (2.8–6.1) months for patients treated using the classical strategy, and 2.0 (1.4–3.7) months for patients treated using the liver-first strategy (P < 0.001).

A total of 281 patients had primary rectal cancer, of which 115 (41%) were handled with the classical strategy and 166 (59%) with the liver-first strategy. The patient characteristics are shown in Table 2. The overall five-year survival was the same, regardless of surgical approach (51% vs 47%, P = 0.474).

A total of 342 patients had primary colon cancer, 262 (77%) of which were treated with the classical strategy and 80 (23%) with the liver-first strategy. The patient characteristics are shown in Table 3. The five-year overall survival was the same in the groups with primary colon cancer (56% vs 51%, P = 0.564).

Eighty-four patients underwent liver resection but not bowel resection. The patient characteristics are shown in Table 4. The overall five-year survival was 14 (8–28)%.

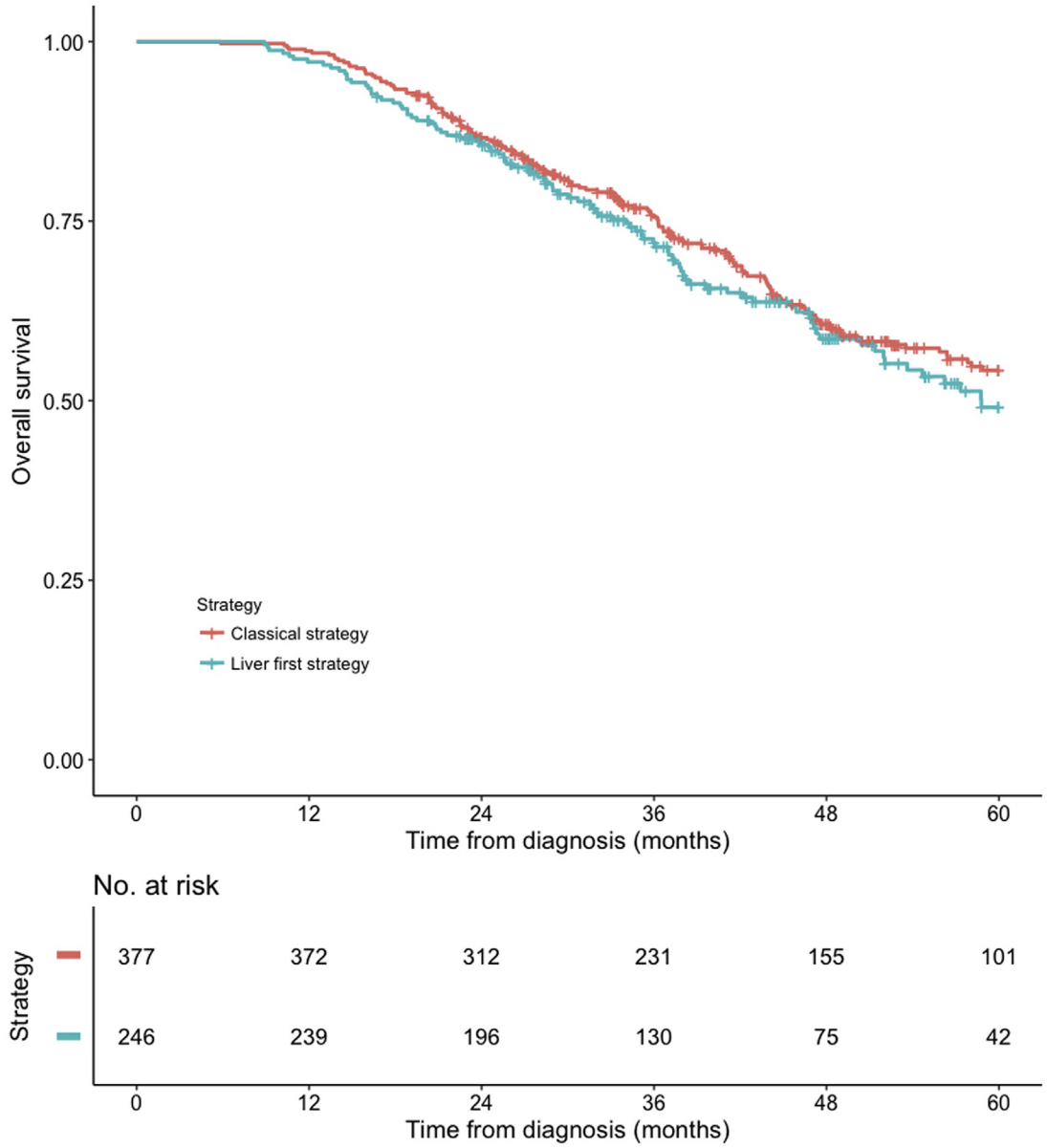

Figure 1 Overall survival from diagnosis for resected patients with synchronous liver metastases, P = 0.34 (log-rank test)

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Table 2 Characteristics of resected patients with primary rectal cancer

	Classical strategy	Liver-first strategy	P‡
Number of patients	115	166	
Gender (Male)	74 (64)	114 (69)	0.519
Age (years)*	65 (58–70)	64 (54–69)	0.070§
ASA score (3–4)	22 (20)	39 (24)	0.463
BMI (kg/m^2)*	25 (23–27)	25 (22–27)	0.572§
Chemotherapy before first resection	55 (48)	145 (88)	<0.001
Radiotherapy before bowel resection	82 (71)	148 (89)	<0.001
T4 primary tumour	13 (12)	14 (9)	0.416
Lymph node positive primary tumour	77 (68)	93 (56)	0.060
R0 primary tumour resection	99 (88)	145 (88)	1.000
Liver TBS*	3.2 (2.2–4.5)	3.6 (2.4–5.6)	0.053§
Major liver resection	39 (35)	80 (50)	0.014
RO liver resection	77 (84)	114 (84)	1.000

Values in parentheses are percentages unless indicated otherwise: *values are median (interquartile range). ASA, American Society of Anesthesiologists; BMI, body mass index; R0, radical resection; TBS, tumour burden score. ‡Fischer's exact test, except §Mann–Whitney U test.

A uni- and multivariate Cox PH models were made with nine independent variables, as shown in Table 5.

Discussion

The liver-first strategy, as introduced by Mentha *et al.*,[6] includes preoperative chemotherapy, resection of colorectal liver metastases, followed by resection of the primary bowel cancer in a second stage. Patients have been increasingly selected for liver-first strategy in the last decade. The present study gives a contemporary analysis of patients with colorectal cancer and synchronous liver metastases, operated for liver metastases in Sweden. Patients chosen for the liver-first strategy were significantly younger, less frequently had positive lymph nodes of the primary tumour, and frequently underwent a major liver resection as compared to patients chosen for the classical strategy. In addition, the liver-first group more often had a primary rectal cancer and underwent preoperative radio-chemotherapy for their primary cancer. It is theoretically appealing to use the waiting time between radio-chemotherapy and resection of the rectal cancer for interval resection of the liver metastases to decrease the risk of tumour progression in the liver and to decrease the total treatment time.[15] Actually, as shown in the present study, the majority of patients with rectal cancer and sCRLM, are chosen for the liver-first strategy in Sweden.

Table 3 Characteristics of resected patients with primary colon cancer

	Classical strategy	Liver-first strategy	P‡
Number of patients	262	80	
Gender (Male)	160 (61)	47 (59)	0.794
Age (years)*	66 (58–73)	61 (54–69)	0.001§
ASA score 3–4	52 (20)	18 (23)	0.638
BMI (kg/m^2)*	26 (23–28)	25 (23–27)	0.274§
Chemotherapy before first resection	42 (16)	75 (95)	<0.001
Radiotherapy before bowel resection	2 (1)	5 (6)	0.009
T4 primary tumour	72 (28)	21 (26)	0.886
Lymph node positive primary tumour	187 (71)	56 (70)	0.888
R0 primary tumour resection	245 (94)	76 (96)	0.584
Liver TBS*	3.8 (2.4–5.4)	5.4 (3.2–7.6)	<0.001§
Major liver resection	113 (44)	45 (57)	0.053
R0 liver resection	185 (87)	59 (88)	1.000

Values in parentheses are percentages unless indicated otherwise: *values are median (interquartile range). ASA, American Society of Anesthesiologists; BMI, body mass index; R0, radical resection; TBS, tumour burden score. ‡Fischer's exact test, except §Mann–Whitney U test.

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Table 4 Characteristics of patients that had undergone liver resection

	Liver resection but no bowel resection	Completed liver-first strategy	P‡
Number of patients	84	246	
Gender (Male)	65 (77)	161 (65)	0.043
Age (years)*	66 (58–72)	62 (54–69)	0.007§
ASA score 3–4	16 (19)	57 (23)	0.451
T4 primary tumour (preoperative)	22 (34)	35 (14)	<0.001
Lymph node positive primary tumour (preoperative)	49 (72)	161 (75)	0.637
Primary rectal tumour	63 (75)	166 (67)	0.219
Chemotherapy before liver resection	71 (85)	220 (90)	0.165
Liver TBS*	4.9 (2.8–9.0)	2.5 (4.1–5.0)	<0.001§
Major liver resection	35 (52)	125 (52)	1.000
R0 liver resection	39 (66)	173 (86)	0.002

Values in parentheses are percentages unless indicated otherwise: *values are median (interquartile range). ASA, American Society of Anesthesiologists; R0, radical resection; TBS, tumour burden score. ‡Fischer's exact test, except §Mann–Whitney U test.

The time between resections was found to be shorter in the liver-first group. However, information about the duration of chemotherapy is lacking in the registries used, making it impossible to analyse total treatment times. No detailed information about chemotherapy protocols is included in the registries. During the study period, national guidelines recommended perioperative oxaliplatin-based chemotherapy.

The liver TBS has previously been described by Sasaki *et al.*, and has shown a prognostic discriminatory power and may even be used for calculating survival benefit.[14] The concept is similar to the 'metro ticket' prognostic system introduced for liver transplantation for hepatocellular carcinoma.[16] The liver-first group had more advanced liver TBS, most probably illustrating that the liver-first strategy is increasingly applied when patients present with advanced liver metastases and an asymptomatic primary tumour. The rationale behind that is to first resect the tumours judged the most threatening to the patient's life.

No survival difference was found between the groups. These findings are in accordance with most previous studies.[7–10] However, Welsh *et al.* published a single centre study with 98 patients in the liver-first strategy group and 467 in the classical strategy group, and found that overall survival was significantly worse for the liver-first group. But after adjusting for the more severe liver disease in the liver-first group no survival difference was found.[10] As no survival benefit has been demonstrated for either strategy, future studies should focus more on the drop-out rate from the intended treatment strategy, the total treatment time, as well as patient-reported outcomes in terms of quality of life. In the present study, the follow-up time may have been too short to be able to detect smaller differences in survival between groups given the modern powerful chemotherapy regimens available in case of recurrence. Recurrence was however not possible to retrieve from the registries.

In the present study, the liver-first and the classical groups were subdivided into groups with primary colon and rectal cancer but again, no overall survival difference was found between the liver-first and the classical groups. The liver-first group with primary colon cancer were younger, more frequently had neoadjuvant therapy, and had more advanced liver TBS as compared to the classical strategy group with primary colon cancer (Table 3).

Of the patients planned for the liver-first strategy, 84 patients (25%) underwent liver resection but not bowel resection. The reasons for this are unclear but a previous study showed that up to 35% of patients with sCRLM do not complete the intended treatment of liver and bowel resections, most commonly because of disease progression.[17] The patients who only underwent liver resection more frequently had clinical T4 primary tumours, more advanced liver TBS, and less often had radical resection margins after liver resection as compared to patients that completed the two resections in the liver-first group (Table 4). From the registries used, it is not possible to deduce the number of patients planned for the classical strategy who then failed to undergo liver resection (intention-to -treat). Previous data from a single centre study in Sweden suggests that the drop-out rate is similar regardless of whether the classical or the liver-first strategy is used.[17]

With Cox PH analysis for the whole group no difference in overall survival for the treatment strategy was found but lymph node-positive primary, T4 primary, high liver TBS and an ASA score 3–4 negatively affected survival (Table 5). All these factors have been previously described.[14,18,19]

Although based on prospectively registered data, a shortcoming of this study is that it is non-randomized. There is therefore a high risk of selection bias. To estimate the influence of the chosen strategy on survival the well established statistical Cox PH model was chosen.[20] An alternative would have been to use

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Table 5 Uni- and multivariate Cox proportional hazards model analysis of overall survival

	Cox univariate HR (95% CI)	P	Cox multivariate HR (95% CI)	P
Treatment				
Classical strategy	Ref		Ref	
Liver-first strategy	1.13 (0.87–1.47)	0.344	1.09 (0.80–1.50)	0.576
Age (years)				
<60	Ref		Ref	
≥60–70	0.83 (0.61–1.13)	0.240	0.81 (0.57–1.17)	0.259
≥70	1.29 (0.95–1.76)	0.107	1.25 (0.87–1.81)	0.231
Gender				
Male	Ref		Ref	
Female	1.05 (0.8–1.36)	0.735	1.06 (0.78–1.43)	0.725
Lymph node positive primary tumour				
No	Ref		Ref	
Yes	1.81 (1.35–2.45)	<0.001*	1.69 (1.21–2.36)	0.002*
T4 primary tumour				
No	Ref		Ref	
Yes	2.00 (1.49–2.69)	<0.001*	1.77 (1.25–2.52)	0.001*
Primary tumour localization				
Colon	Ref		Ref	
Rectum	1.06 (0.82–1.36)	0.674	1.15 (0.84–1.58)	0.370
TBS				
<3	Ref		Ref	
≥3–9	1.3 (0.96–1.75)	0.086	1.26 (0.91–1.75)	0.157
≥9	1.95 (1.22–3.12)	0.005*	1.67 (1.01–2.78)	0.047*
ASA score				
1–2	Ref		Ref	
3–4	1.68 (1.26–2.24)	<0.001*	1.81 (1.31–2.49)	<0.001*
BMI (kg/m^2)				
<25	Ref		Ref	
≥25–35	1.06 (0.81–1.38)	0.695	1 (0.75–1.35)	0.974
≥35	1.6 (0.74–3.43)	0.231	1.3 (0.59–2.87)	0.520

Data are presented as hazard ratio (95% confidence interval). HR, hazard ratio; CI, confidence interval; TBS, Tumour burden score. ASA, American Society of Anesthesiologists; BMI, body mass index; Ref, reference. Asterisk values indicate $P < 0.05$.

propensity score matching. Propensity score matching is known to have the ability to decrease imbalance, model dependence, and bias. However, a regression model is often more powerful than propensity score matching in detecting differences in treatment effect.[20,21]

The strength of this study is that this is a population-based study, thus reflecting the results of how these patients are managed today in Sweden. Furthermore, this is the largest patient cohort presented to date.

In conclusion, in this population-based study, patients chosen for the liver-first strategy had more often rectal primary tumours, advanced liver disease and less often node-positive primaries. Survival did not differ when compared to patients undergoing the classical strategy.

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Conflict of interest statement

Authors have no commercial interest to disclose.

References

1. Parkin DM, Bray F, Ferlay J, Pisani P. (2002) Global cancer statistics, 2002. *CA Cancer J Clin* 55:74–108.
2. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M *et al*. (2015) Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 136:E359–E386.
3. Riihimäki M, Hemminki A, Sundquist J, Hemminki K. (2016) Patterns of metastasis in colon and rectal cancer. *Sci Rep* 6:29765.

Please cite this article in press as: Valdimarsson VT, et al., Outcomes of liver-first strategy and classical strategy for synchronous colorectal liver metastases in Sweden, HPB (2017), https://doi.org/10.1016/j.hpb.2017.11.004

4. Leporrier J, Maurel J, Chiche L, Bara S, Segol P, Launoy G. (2006) A population-based study of the incidence, management and prognosis of hepatic metastases from colorectal cancer. *Br J Surg* 93:465–474.
5. Manfredi S, Lepage C, Hatem C, Coatmeur O, Faivre J, Bouvier A-M. (2006) Epidemiology and management of liver metastases from colorectal cancer. *Ann Surg* 244:254–259.
6. Mentha G, Majno PE, Andres A, Rubbia-Brandt L, Morel P, Roth AD. (2006) Neoadjuvant chemotherapy and resection of advanced synchronous liver metastases before treatment of the colorectal primary. *Br J Surg* 93:872–878.
7. Jegatheeswaran S, Mason JM, Hancock HC, Siriwardena AK. (2013) The liver-first approach to the management of colorectal cancer with synchronous hepatic metastases: a systematic review. *JAMA Surg* 148: 385–391.
8. Kelly ME, Spolverato G, Le GN, Mavros MN, Doyle F, Pawlik TM *et al*. (2015) Synchronous colorectal liver metastasis: a network meta-analysis review comparing classical, combined, and liver-first surgical strategies. *J Surg Oncol United States* 111:341–351.
9. Baltatzis M, Chan AKC, Jegatheeswaran S, Mason JM, Siriwardena AK. (2016) Colorectal cancer with synchronous hepatic metastases: systematic review of reports comparing synchronous surgery with sequential bowel-first or liver-first approaches. *Eur J Surg Oncol England* 42:159–165.
10. Welsh FKS, Chandrakumaran K, John TG, Cresswell AB, Rees M. (2016) Propensity score-matched outcomes analysis of the liver-first approach for synchronous colorectal liver metastases. *Br J Surg* 103:600–606.
11. Andres A, Toso C, Adam R, Barroso E, Hubert C, Capussotti L *et al*. (2012) A survival analysis of the liver-first reversed management of advanced simultaneous colorectal liver metastases: a LiverMetSurvey-based study. *Ann Surg* 256:772–778 [discussion 778–779].
12. Kodeda K, Nathanaelsson L, Jung B, Olsson H, Jestin P, Sjövall A *et al*. (2013) Population-based data from the Swedish Colon Cancer Registry. *Br J Surg* 100:1100–1107.
13. Årsrapport nationellt kvalitetsregister. (2016) *Cancer i lever och gallvägar* [Internet]. [cited 2017 Apr 12]. Available from: http://www.cancercentrum.se/globalassets/cancerdiagnoser/lever-och-galla/kvalitetsregister/sweliv_rapport_2015_final.pdf.
14. Sasaki K, Morioka D, Conci S, Margonis GA, Sawada Y, Ruzzenente A *et al*. (2016) The tumor burden score: a new "metro-ticket" prognostic tool for colorectal liver metastases based on tumor size and number of tumors. *Ann Surg*. https://doi.org/10.1097/SLA.0000000000002064.
15. Adam R, de Gramont A, Figueras J, Kokudo N, Kunstlinger F, Loyer E *et al*. (2016) Managing synchronous liver metastases from colorectal cancer: a multidisciplinary international consensus. *Cancer Treat Rev* 41:729–741.
16. Mazzaferro V, Llovet JM, Miceli R, Bhoori S, Schiavo M, Mariani L *et al*. (2009) Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis. *Lancet Oncol* 10:35–43.
17. Sturesson C, Valdimarsson VT, Blomstrand E, Eriksson S, Nilsson JH, Syk I *et al*. (2017) Liver-first strategy for synchronous colorectal liver metastases – an intention-to-treat analysis. *HPB* 19:1–7.
18. Fong Y, Fortner J, Sun RL, Brennan MF, Blumgart LH. (1999) Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer analysis of 1001 consecutive cases. *Ann Surg* 230: 309–318 [discussion 318–321].
19. van Amerongen MJ, van der Stok EP, Fütterer JJ, Jenniskens SFM, Moelker A, Grünhagen DJ *et al*. (2016) Short term and long term results of patients with colorectal liver metastases undergoing surgery with or without radiofrequency ablation. *Eur J Surg Oncol* 42:523–530.
20. Biondi-Zoccai G, Romagnoli E, Agostoni P, Capodanno D, Castagno D, D'Ascenzo F *et al*. (2011) Are propensity scores really superior to standard multivariable analysis? *Contemp Clin Trials* 32: 731–740.
21. Brazauskas R, Logan BR. (2016) Observational studies: matching or regression? *Biol Blood Marrow Transplant Elsevier* 22:557–563.

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