Original article

Significance of the surgical hepatic resection margin in patients with a single hepatocellular carcinoma

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Background: **The impact of a wide surgical margin on the outcome of patients with hepatocellular carcinoma (HCC) has not been evaluated in relation to the type of liver resection performed, anatomical or non-anatomical. The aim of this study was to evaluate the impact of surgical margin status on outcomes in patients undergoing anatomical or non-anatomical resection for solitary HCC.**

Methods: **Data from patients with solitary HCC who had undergone non-anatomical partial resection (Hr0 group) or anatomical resection of one Couinaud segment (HrS group) between 2000 and 2007 were extracted from a nationwide survey database in Japan. Overall and recurrence-free survival associated with the surgical margin status and width were evaluated in the two groups.**

Results: **A total of 4457 patients were included in the Hr0 group and 3507 in the HrS group. A microscopically positive surgical margin was associated with poor overall survival in both groups. A negative but 0-mm surgical margin was associated with poorer overall and recurrence-free survival than a wider margin only in the Hr0 group. In the HrS group, the width of the surgical margin was not associated with patient outcome.**

Conclusion: **Anatomical resection with a negative 0-mm surgical margin may be acceptable. Non-anatomical resection with a negative 0-mm margin was associated with a less favourable survival outcome.**

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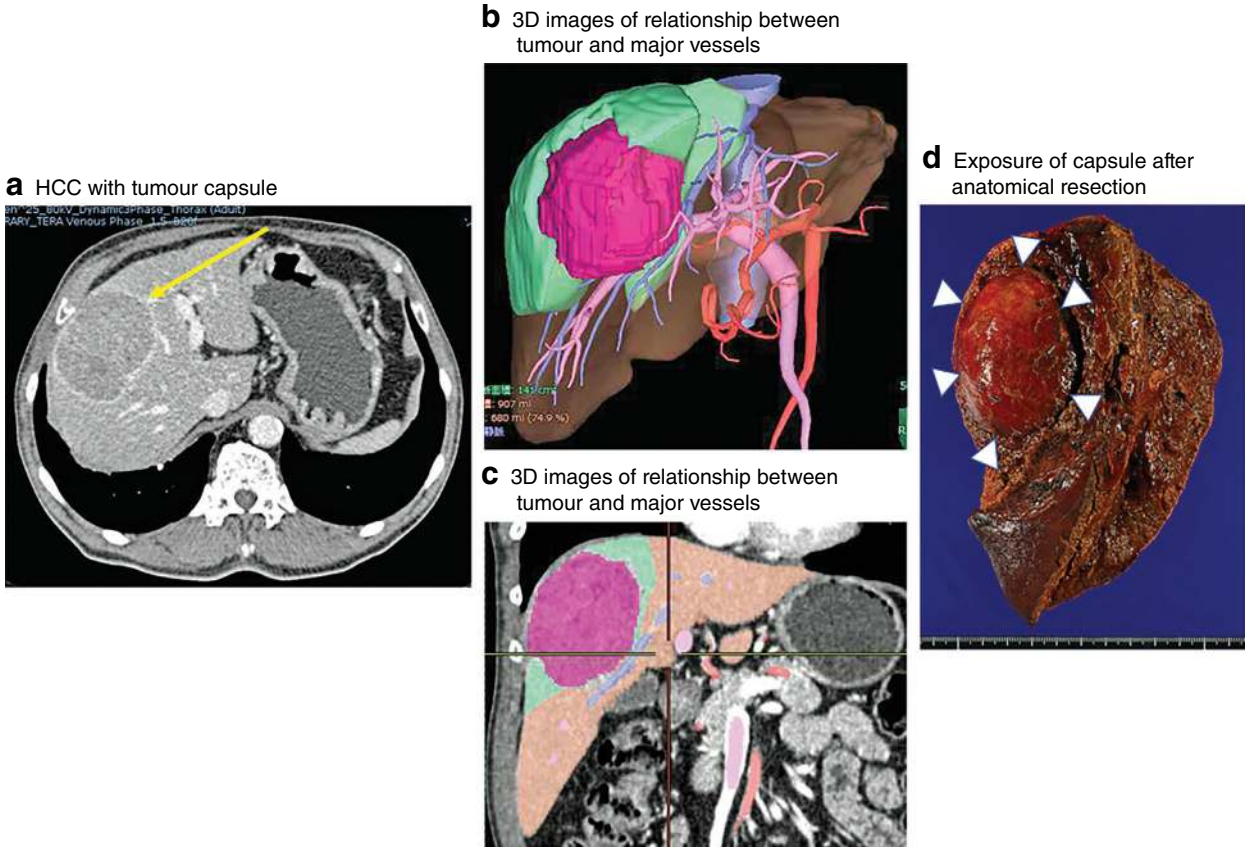
Introduction

Surgical resection remains the mainstay of treatment for hepatocellular carcinoma (HCC). However, the indications and feasibility of operative procedures are restricted by both tumour characteristics and functional liver reserve, as most patients with HCC have underlying chronic liver disease.

Regarding operative procedures for curative resection of HCC, some authors[1–10] have emphasized that anatomical resection (complete removal of tumour-bearing portal territory) should be done whenever feasible. The reason for this is supported theoretically by the perspective that HCC tumour cells spread through the portal venous system[11]. However, others[12,13] have stressed the importance of the width of the surgical margin, arguing that anatomical resection is not necessarily required when a wide (more than 1 cm) tumour-free surgical margin can be attained. Furthermore, although a recent meta-analysis[14] demonstrated a survival benefit for anatomical resection, some case–control studies[15–17] using propensity score matching have failed to show this benefit.

Following anatomical resection of the liver, hepatic venous tributaries running between liver segments/subsegments and/or the hepatic hilum appear on the cut surface of the liver. Therefore, when the HCC

Fig. 1 Imaging and pathological appearance of hepatocellular carcinoma attaching to a major hepatic vein



a Hepatocellular carcinoma (HCC) with tumour capsule located adjacent to the middle hepatic vein (arrow). **b,c** The relationship between the tumour and major vessels is presented using simulation three-dimensional (3D) software (SYNAPSE VINCENT®; Fujifilm, Tokyo, Japan). **d** After performing an anatomical resection, the tumour capsule is exposed on the raw surface of the resected specimen (arrows).

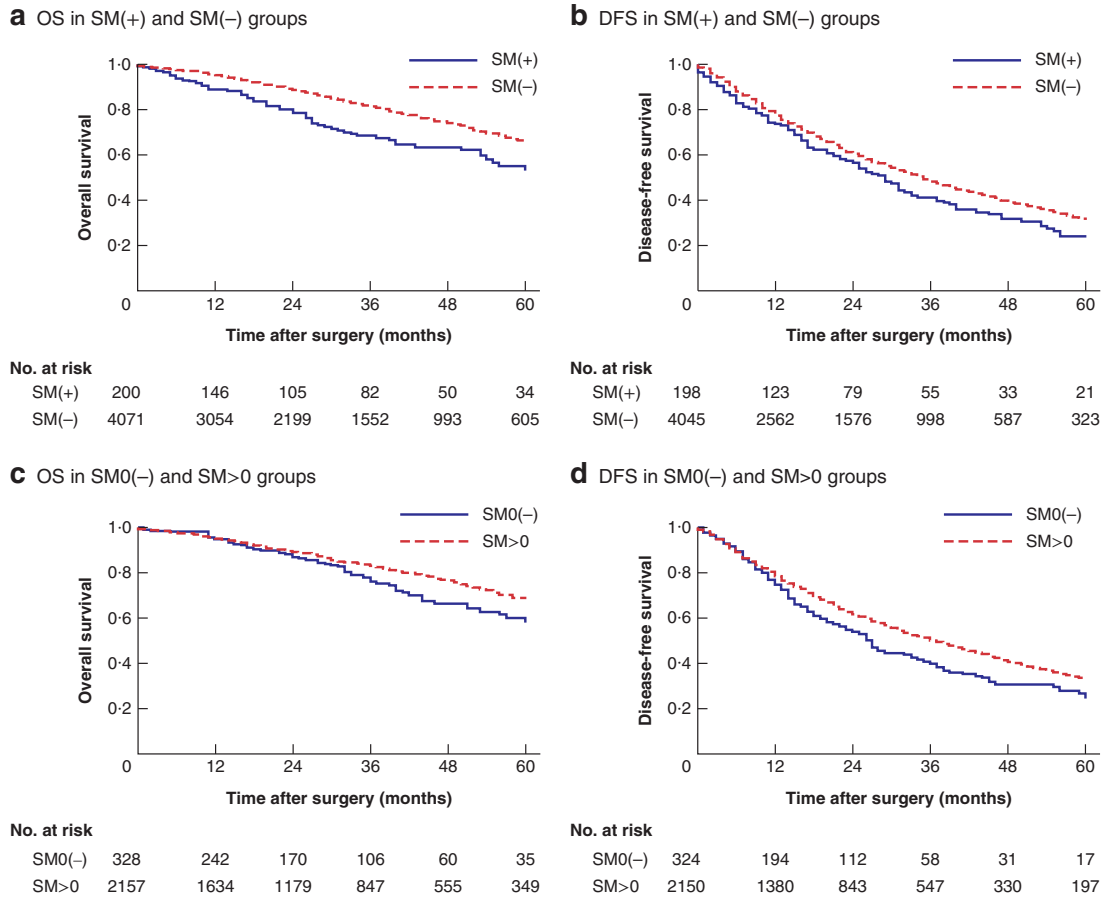
is attached to a major hepatic vein and/or the hepatic hilum, the tumour capsule is exposed on the raw surface of the resected specimen (*Fig. 1a–d*). As most classical HCCs have tumour capsules, such a situation does not necessarily indicate a microscopically positive surgical margin (SM(+)), although the width of the surgical margin is 0 mm (denoted as SM0(–)). Such a situation may also happen during non-anatomical partial resections aimed at preserving as much of the functioning liver parenchyma as possible, especially in patients with cirrhosis. However, the impact of SM0(–) status has not yet been clarified[18].

In the present study, the significance of the surgical margin in patients with HCC undergoing anatomical or non-anatomical partial resection was investigated using nationwide survey data. Special attention was paid to the impact of SM0(–) status on the outcomes of anatomical resection.

Methods

The Liver Cancer Study Group of Japan has been conducting biannual nationwide surveys of patients with primary liver cancer since 1965, and has updated the survival data of enrolled patients. More than 600 institutions in Japan have participated in the surveys, with the approval of each institution, and have answered more than 180 questionnaires regarding patient characteristics, diagnostic findings, treatment selection, treatment findings and patient outcomes. In the first step, physicians at the participating institutions completed the questionnaire and checked the accuracy of the data. In the second step, the nationwide survey committee checked the data; whenever there were unusual data, the participating institution was requested to confirm the data to ensure their accuracy.

Fig. 2 Overall and disease-free survival in patients with hepatocellular carcinoma who had a non-anatomical partial resection



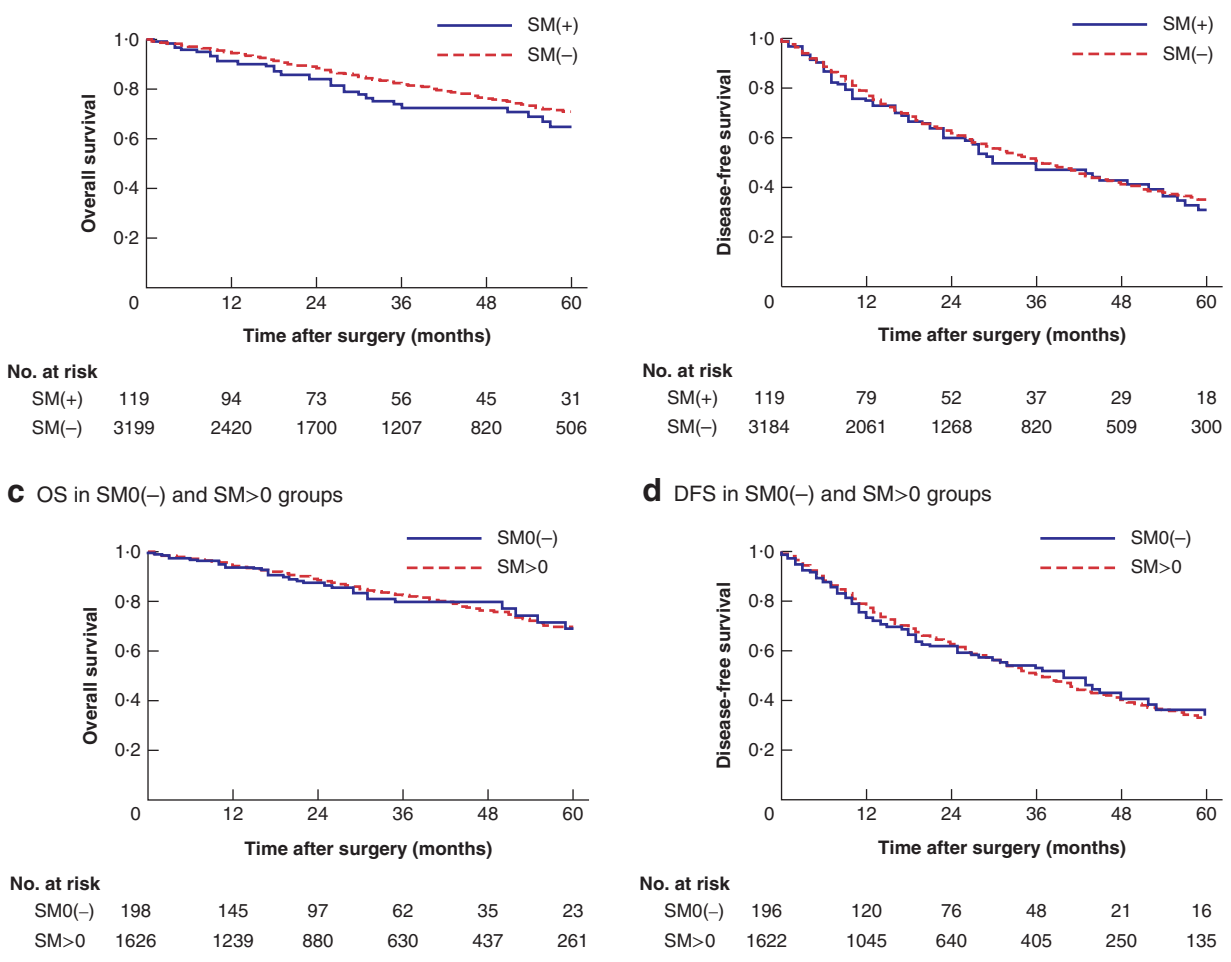
a Overall (OS) and **b** disease-free (DFS) survival curves comparing patients who had a non-anatomical partial resection (Hr0) with a positive (SM(+)) or negative (SM(–)) surgical margin. **c** OS and **d** DFS curves comparing patients in the Hr0 SM(–) subgroup who had a surgical margin width of 0 mm (SM0(–)) or greater than 0 mm (SM > 0). **a** $P < 0{\cdot}001$, **b** $P = 0{\cdot}050$, **c** $P = 0{\cdot}042$, **d** $P = 0{\cdot}004$ (log rank test).

Table 1 Background parameters in patients who had a non-anatomical partial resection with surgical margin width of 0 mm or greater than 0 mm

	Hr0 SM0(–) ($n = 334$)	Hr0 SM > 0 ($n = 2202$)	P†
Total bilirubin (mg/dl)*	0·83(±0·38)	0·87(1·34)	0·554
Albumin (g/dl)*	3·80(0·51)	3·84(0·49)	0·255
Prothrombin time (%)*	85·1(13·2)	84·8(15·3)	0·775
Platelet count ($\times 10^4$/μl)*	13·3(7·3)	13·3(6·3)	0·870
ICGR15 (%)*	19·6(11·0)	18·6(11·1)	0·109
Child–Pugh grade	$n = 330$	$n = 2007$	0·516‡
A	289	1751	
B	41	248	
C	0	8	
Tumour size (cm)*	3·47(2·07)	3·65(3·76)	0·408

*Values are mean(s.d.). Hr0, resection of less than one Couinaud segment (non-anatomical partial resection); SM0(–), negative surgical margin of width 0 mm; SM > 0, surgical margin width greater than 0 mm; ICGR15, indocyanine green retention rate at 15 min. †Student's t test, except ‡χ^2 test.

Fig. 3 Overall and disease-free survival in patients with hepatocellular carcinoma who had an anatomical resection



a Overall (OS) and **b** disease-free (DFS) survival curves comparing patients who had an anatomical resection (HrS) with a positive (SM(+)) or negative (SM(–)) surgical margin. **c** OS and **d** DFS curves comparing patients in the HrS SM(–) subgroup who had a surgical margin width of 0 mm (SM0(–)) or greater than 0 mm (SM > 0). **a** $P = 0{\cdot}053$, **b** $P = 0{\cdot}498$, **c** $P = 0{\cdot}969$, **d** $P = 0{\cdot}904$ (log rank test).

Patients

Data collected from the 16th, 17th, 18th and 19th Liver Cancer Study Group of Japan nationwide surveys (2000–2007) were used. Among new patients registered during the study period, those fulfilling the following criteria were extracted: a solitary tumour detected on imaging; histopathologically proven HCC; and treated by hepatic resection with curative intent. In addition, the extent of hepatic resection was investigated, and patients who had undergone partial resection of less than one Couinaud segment[19] (Hr0 group) and those who had had resection of one Couinaud segment (HrS group) were identified. These patients served as the population for the present study. In the survey, the surgical method employed for a segmentectomy (such as staining technique, hilar approach and compression technique) was not investigated.

In the Hr0 and HrS groups, the surgical margin status (SM(+) or SM(–)) and the width of the surgical margin were investigated. In particular, patients with a surgical margin of 0 mm, with exposure only of the tumour capsule, were defined as having SM0(–), and were assessed separately. The relationship between margin status and patient outcomes was evaluated.

Table 2 Background parameters in patients who had an anatomical resection with surgical margin width of 0 mm or greater than 0 mm

	HrS SM0(–) (n = 201)	HrS SM > 0 (n = 1664)	P†
Total bilirubin (mg/dl)*	0·81(0·30)	0·80(0·46)	0·782
Albumin (g/dl)*	3·88(0·51)	3·09(0·48)	0·719
Prothrombin time (%)*	86·1(14·3)	86·7(15·2)	0·624
Platelet count (× 10^4/μl)*	14·9(6·3)	14·9(6·7)	0·961
ICGR15 (%)*	15·8(8·7)	15·7(9·6)	0·988
Child–Pugh grade	n = 196	n = 1614	0·991‡
A	177	1469	
B	18	142	
C	1	3	
Tumour size (cm)*	4·26(2·57)	3·63(2·72)	0·002
AFP (ng/ml)*	2441(9433)	1686(6804)	0·330
PIVKA-II (munits/ml)*	1069(1741)	885(1607)	0·269
Tumour differentiation	n = 193	n = 1560	< 0·001‡
Well	157	1416	
Moderate/poor	36	144	

*Values are mean(s.d.). HrS, resection of one Couinaud segment (anatomical resection); SM0(–), negative surgical margin of width 0 mm; SM > 0, surgical margin width greater than 0 mm; ICGR15, indocyanine green retention rate at 15 min; AFP, α-fetoprotein; PIVKA-II, protein induced by vitamin K antagonist II. †Student's t test, except ‡χ^2 test.

Statistical analysis

Background liver function parameters and tumour characteristics were compared using the Student's t test, Mann–Whitney U test or the χ^2 test, as appropriate. Survival curves were generated using the Kaplan–Meier method and compared with the log rank test. Cut-off values of the width of the surgical margin for recurrence-free survival and overall survival (OS) were identified using receiver operating characteristic (ROC) curve analysis. To examine significant factors for OS and disease-free survival (DFS) in the Hr0 and SM(–) groups, Cox proportional hazard models were generated. Analyses were conducted using IBM SPSS® version 24 (IBM, Armonk, New York, USA) and BellCurve for Excel (Social Survey Research Information, Tokyo, Japan). Differences were considered significant at $P < 0·050$.

Results

During the study interval, 83 540 new patients with HCC were registered and followed up prospectively. Data for 14 075 patients who met the inclusion criteria were extracted, 4457 in the Hr0 group and 3507 in the HrS group. The remaining 6111 patients had undergone other surgical procedures, and were excluded.

Analysis of patients having non-anatomical partial resection

Among the 4457 patients in the Hr0 group, the surgical margin was microscopically positive (SM(+)) in 204, microscopically negative (SM(–)) in 4178, and unknown in 75. OS in the SM(+) group was significantly lower than in the SM(–) group ($P < 0·001$) (*Fig. 2a*), and DFS also showed a tendency to more unfavourable survival ($P = 0·050$) (*Fig. 2b*).

In the 4178 patients with SM(–) status, the width of the surgical margin was 0 mm (SM0(–)) in 334 patients, more than 0 mm (SM > 0) in 2202, and unknown in 1642. Background liver function parameters, including serum total bilirubin level, serum albumin level, plasma prothrombin time, platelet count, indocyanine green retention rate at 15 min (ICGR15), Child–Pugh grade and tumour size, were comparable in SM0(–) and SM > 0 groups (*Table 1*). However, OS and DFS rates were lower in the SM0(–) group than in the SM > 0 group ($P = 0·042$ and $P = 0·004$ respectively) (*Fig. 2c,d*). When patients were grouped according to the width of the surgical margin into four subgroups (0, 1–5, 6–10 and 11 mm or more), it was found that the higher the width of the surgical margin, the greater the tendency was towards favourable OS and better DFS ($P = 0·076$ and $P = 0·007$ respectively) (*Fig. S1*, supporting information).

To identify the cut-off surgical margin in the Hr0 group, ROC curves were generated for OS and DFS (*Fig. S2*, supporting information). However, a precise cut-off value could not be determined.

Univariable and multivariable analyses were performed to explore variables associated with OS and DFS in the Hr0 SM(–) group. SM > 0 was independently associated with both OS and DFS (*Tables S1* and *S2*, supporting information).

Analysis of patients having anatomical resection

Among the 3507 patients in the HrS group, the surgical margin was microscopically positive (SM(+)) in 124 patients, microscopically negative (SM(−)) in 3305, and unknown in 78. A tendency towards a lower OS rate was observed in the SM(+) group compared with the SM(−) group ($P = 0{\cdot}053$) (*Fig. 3a*), although DFS rates in both groups were comparable ($P = 0{\cdot}498$) (*Fig. 3b*).

Of the 3305 patients with a negative surgical margin, 201 had SM0(−) status, 1664 had SM > 0 status, and the margin status was unknown in 1440. Serum total bilirubin level, serum albumin level, plasma prothrombin time, platelet count, ICGR15, Child–Pugh grade and tumour marker values were similar in SM0(−) and SM > 0 groups. However, tumour size was significantly greater in the SM0(−) group, which also included more poorly differentiated tumours (*Table 2*). OS and DFS rates were comparable between the two groups ($P = 0{\cdot}969$ and $P = 0{\cdot}904$ respectively) (*Fig. 3c,d*).

Discussion

This study has shown that the significance of surgical margin status and width is different in patients undergoing anatomical resection (HrS group) and non-anatomical partial resection (Hr0 group). A microscopically positive surgical margin was associated with unfavourable patient outcomes in both HrS and Hr0 groups. However, in patients with a microscopically negative surgical margin, the impact of surgical margin width on patient outcomes was different.

In the Hr0 group, survival outcomes in patients with SM0(−) status were poorer than those in patients with SM > 0 status, even though background liver functional data and tumour status were comparable in these two subgroups. In addition, when the patients were divided into four subgroups according to the width of the surgical margin, a greater margin width was associated with better OS and DFS, suggesting that a greater surgical margin reduces the risk of local recurrence.

However, in the HrS group, outcomes of patients with SM0(−) status were similar to those of patients with SM > 0 status, even though mean tumour size was greater in the SM0(−) group and the SM0(−) group included more poorly differentiated tumours. These results may indicate that, when performing a non-anatomical resection, the impact of surgical margin width is less than that for an anatomical resection. When the HCC is attached to a major hepatic vein and/or the hepatic hilum, liver resection preserving the attached vessel/hepatic hilum, with exposure of the tumour capsule, is acceptable when an anatomical resection is attained.

A major aim of surgical resection in patients with HCC is to extirpate the tumour while ensuring a pathologically negative margin, and to clear portal vein invasion and/or prevent potential spread of intrahepatic metastases around the tumour. Previous studies[20–22] have documented that most portal vein invasion and intrahepatic micrometastases are found within 10 mm of the main tumour, and rarely more than 20 mm from the tumour. Thus, these authors concluded that a minimum surgical margin width of 10 mm was required, even though the surgical procedure (anatomical or non-anatomical resection) was not referred to. A recent study[23], which reproduced the distribution of portal vein invasion and/or intrahepatic metastasis on preoperative three-dimensional CT images, revealed that almost all portal vein invasion and intrahepatic metastases were localized to the peritumoral area within 10 mm of the margin in HCCs smaller than 3 cm in diameter. However, portal vein invasion and intrahepatic metastases spread to the feeding third-level portal branches in HCCs more than 3 cm in diameter. In addition, three-dimensional mapping images have suggested that portal vein invasion and/or intrahepatic metastasis had spread through the portal territories, not radially in all directions[23]. These findings, obtained using an advanced imaging simulation software, may support the present results that the width of the surgical margin has no effect on outcomes in patients undergoing complete anatomical resection. In contrast, when performing a non-anatomical partial resection, clearance of portal vein invasion and/or intrahepatic metastasis is dependent on the extent of the area co-resected with the main tumour, especially in the direction along the portal pedicle feeding the tumour. This implies that a non-anatomical partial resection could have similar ability to anatomical resection in preventing intrahepatic recurrence, if there is a wide surgical margin. The present results in the Hr0 group may lend support to this hypothesis.

Recently, Oguro and colleagues[24] studied the significance of macroscopic 'no-margin' hepatectomy for HCC. Their results were similar to those found in the present study: no-margin operations did not have a negative impact on patient outcome when a microscopically negative surgical margin could be secured. Their report was based on a single-centre experience, and an advantage of their investigation was the uniformity of operative procedures and pathological evaluation. Although the present results were based on heterogeneous nationwide survey data, the authors believe that analyses of the data from a large cohort of over 3000 patients can elicit valid conclusions.

As mentioned, previous reports[20–23] have recommended a surgical margin of at least 10 mm in non-anatomical partial resections. In addition, an RCT[25] has shown that

partial hepatectomy with a margin of 2 cm is superior to a margin of 1 cm in terms of tumour-related mortality. In the present analysis, ROC curves were constructed, but the minimum width of the surgical margin required when performing non-anatomical partial resection could not be determined. It may be speculated that the required surgical margin may be dependent on tumour status (tumour size and/or invasiveness) and that clear cut-off values for the surgical margin cannot be determined. Further analysis is required to resolve this issue after extracting small, more homogeneous, portions of the patient cohort.

In the HrS group, a tendency towards a lower OS rate was observed in the SM(+) group than in the SM(−) group. However, DFS rates in these two groups were similar. These results may seem difficult to interpret, as a positive surgical margin generally affects DFS. The present study examined the content of main treatments after recurrence (re-resection, ablation, transcatheter arterial chemoembolization, etc.) in the two groups, but the results were similar. One possible explanation for these paradoxical results may be the small number of patients with SM(+) status in the HrS group.

There are some limitations to the present study, associated mainly with the nature of nationwide survey data. The indications for anatomical and non-anatomical resection were heterogeneous among institutions, and so the results of anatomical and non-anatomical resections were not compared. In addition, the clinical course of each patient could not be tracked. As a result, it was impossible to assess the treatments performed after recurrence, and only OS was evaluated after the primary resection.

Acknowledgements

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The context of this study was presented to the American Association for the Study of Liver Disease Liver Meeting, Washington, D.C., USA, October 2017.

Disclosure: The authors declare no conflict of interest.

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Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the article.

European Colorectal Congress

28 November – 1 December 2022, St.Gallen, Switzerland

Monday, 28 November 2022

09.50
Opening and welcome
Jochen Lange, St.Gallen, CH

10.00
It is leaking! Approaches to salvaging an anastomosis
Willem Bemelman, Amsterdam, NL

10.30
Predictive and diagnostic markers of anastomotic leak
Andre D'Hoore, Leuven, BE

11.00
SATELLITE SYMPOSIUM
ETHICON

11.45
Of microbes and men – the unspoken story of anastomotic leakage
James Kinross, London, UK

12.15
LUNCH

13.45
Operative techniques to reduce anastomotic recurrence in Crohn's disease
Laura Hancock, Manchester, UK

14.15
Innovative approaches in the treatment of complex Crohn Diseases perianal fistula
Christianne Buskens, Amsterdam, NL

14.45
To divert or not to divert in Crohn surgery – technical aspects and patient factors
Pär Myrelid, Linköping, SE

15.15
COFFEE BREAK

15.45
Appendiceal neoplasia – when to opt for a minimal approach, when and how to go for a maximal treatment
Tom Cecil, Basingstoke, Hampshire, UK

16.15
SATELLITE SYMPOSIUM
Medtronic
Further,Together

17.00
Outcomes of modern induction therapies and Wait and Watch strategies, Hope or Hype
Antonino Spinelli, Milano, IT

17.30
EAES Presidential Lecture - Use of ICG in colorectal surgery: beyond bowel perfusion
Salvador Morales-Conde, Sevilla, ES

18.00
Get-Together with your colleagues
Industrial Exhibition

Tuesday, 29 November 2022

9.00
CONSULTANT'S CORNER
Michel Adamina, Winterthur, CH

10.30
COFFEE BREAK

11.00
SATELLITE SYMPOSIUM
INTUITIVE

11.45
Trends in colorectal oncology and clinical insights for the near future
Rob Glynne-Jones, London, UK

12.15
LUNCH

13.45
VIDEO SESSION

14.15
SATELLITE SYMPOSIUM
BD

15.00
COFFEE BREAK

15.30
The unsolved issue of TME: open, robotic, transanal, or laparoscopic – shining light on evidence and practice
Des Winter, Dublin, IE
Jim Khan, London, UK
Brendan Moran, Basingstoke, UK

16.30
SATELLITE SYMPOSIUM
Takeda

17.15
Lars Pahlman lecture
Søren Laurberg, Aarhus, DK

Thursday, 1 December 2022
Masterclass in Colorectal Surgery
Proctology Day

Wednesday, 30 November 2022

9.00
Advanced risk stratification in colorectal cancer – choosing wisely surgery and adjuvant therapy
Philip Quirke, Leeds, UK

09.30
Predictors for Postoperative Complications and Mortality
Ronan O'Connell, Dublin, IE

10.00
Segmental colectomy versus extended colectomy for complex cancer
Quentin Denost, Bordeaux, FR

10.30
COFFEE BREAK

11.00
Incidental cancer in polyp - completion surgery or endoscopy treatment alone?
Laura Beyer-Berjot, Marseille, FR

11.30
SATELLITE SYMPOSIUM

12.00
Less is more – pushing the boundaries of full-thickness rectal resection
Xavier Serra-Aracil, Barcelona, ES

12.30
LUNCH

14.00
Management of intestinal neuroendocrine neoplasia
Frédéric Ris, Geneva, CH

14.30
Poster Presentation & Best Poster Award
Michel Adamina, Winterthur, CH

15.00
SATELLITE SYMPOSIUM
OLYMPUS

15.45
COFFEE BREAK

16.15
Reoperative pelvic floor surgery – dealing with perineal hernia, reoperations, and complex reconstructions
Guillaume Meurette, Nantes, FR

16.45
Salvage strategies for rectal neoplasia
Roel Hompes, Amsterdam, NL

17.15
Beyond TME – technique and results of pelvic exenteration and sacrectomy
Paris Tekkis, London, UK

19.30
FESTIVE EVENING

Information & Registration **www.colorectalsurgery.eu**