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Contemporary practice and short-term outcomes after liver resections in a complete national cohort

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Abstract

Background Improved outcome after liver resections have been reported in several series, but outcomes from national cohorts are scarce. Our aim was to evaluate nationwide practice and short-term outcomes after liver surgery in a universal healthcare system.
Methods A complete 5-year cohort of all liver resections from the Norwegian Patient Registry (NPR). Short-term outcomes were aggregated length of stay (a-LoS), reoperation and 90-day mortality.
Results Of 2118 liver resections, 605 (28.6%) were major, median age was 65 years and 1184 (55%) were male. Most common indication was metastatic disease ($n = 1554$; 73.4%) and primary malignancy ($n = 328$; 15.3%). Laparoscopy was performed in 513 (33.9%) of minor and 37 (6.1%) of major liver resections and increased over time to 39.1% of minor resections in 2016. Median a-LoS was 12 days for major resections, 8 days for open minor and 3 days for laparoscopic minor resections. Reoperation was reported for 159 (7.4%) and 90-day mortality for 44 (2.1%). Primary malignancy, male gender, elderly patients and major resections were associated with poorer outcome.
Conclusions In a national cohort, laparoscopy is used for a substantial proportion of minor resections and was associated with reduced a-LoS. Risk factors for reoperation and mortality were male gender, increased age and major resection for primary malignancy.

Keywords Liver resection · National cohort · Short-term outcomes · Laparoscopic

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Introduction

Liver resections are now performed with low mortality and acceptable morbidity [1]. Factors that have been associated with poorer short-term outcome are male gender, increasing age, low-volume operating institutions, extended resections and resection for a primary liver malignancy [2–5]. Laparoscopic liver surgery is considered both feasible and safe for smaller resections and in easily accessible segments. Laparoscopic major resections are being increasingly performed but largely at specialised, high-volume centres [6–9].

Most data on surgical outcomes are derived from selected case-series or audits which may not represent results in routine practice. Academic and high-volume centres may be overrepresented in single centre series and audits with incomplete coverage and as such may not fully illustrate the situation in all centres. Also, randomised trials usually have exclusion criteria (e.g. older participants) that may result in a patient sample that deviates from populations of routine practice or otherwise unselected cohorts [10]. As a result, reported

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outcomes may be skewed and underestimate the real length of stay as well as the rates of morbidity and mortality following liver-surgery "across the nation" in routine practice. Observational data in the form of complete, population-based cohorts that include "all comers" and all hospitals are suited to assess magnitude of effect rather than establish a cause–effect relationship [11]. Where prospective clinical registries are not available, administrative data may provide data for core variables and outcome.

The aim of this study was to investigate contemporary practice in a complete cohort of patients undergoing liver resection in a country with universal public healthcare coverage and to examine the use of laparoscopy and the impact of established risk factors on short-term outcomes.

Methods

This study was carried out and reported in accordance with the "Strengthening the Reporting of Observational Studies in Epidemiology in Epidemiology" (STROBE) guidelines [12].

Ethics

Centre of Clinical Documentation and Evaluation (SKDE) holds a concession from the Norwegian Data Protection Authority to access data from the Norwegian Patient Registry (NPR) for patients treated at Norwegian hospitals in the period 1 January 2012 to 31 December 2016. The Norwegian Data Inspectorate licenced the data registry at SKDE (ref. 15/00271–2/CGN and 16/00289–2/CGN). Further ethical approval was not required according to Norwegian law.

The Norwegian Patient Registry

The Norwegian Patient Registry (NPR) uses an encrypted serial number that enables individual patient pathways to be tracked from one stay to another, thus allowing for identification of a subsequent readmission or reoperation occurring at a local hospital following transfer from a tertiary hospital where index surgery had been performed. All Norwegian hospitals must submit data to the Norwegian Patient Registry for registry and reimbursement purposes. The selected NPR variables have good data quality and completeness [13] and also illustrate core quality outcome metrics in major surgery as shown for other diseases and cross-cohort analysis [14–16].

Study period and study population

All patients with a procedure code within the NPR denoting surgical resection of the liver in the years of 1 January 2012 to 31 December 2016 were included. This constitutes a complete national 5-year cohort.

The database

The database and the extraction methods have been described in more detail elsewhere [17]. Norway has a universal healthcare program for all citizens (population almost 5.3 million inhabitants per December 2017) that ensure equal access to care. Every citizen has a unique 11-digit social security number that can be tracked between several registries and healthcare records, given appropriate permissions. Norway is divided into four regional health authorities (RHA). Surgery for cancer of the GI/HPB system is exclusively performed by public healthcare hospitals, and liver surgery is only provided at the five university hospitals of Oslo, Stavanger, Bergen, Trondheim and Tromsø.

A database of indications, liver resection procedures (minor or major), access modality (laparoscopic or open), length of stay and rate of re-laparotomy or re-laparoscopy and 90 days mortality was created based on data extracted from the NPR.

Inclusion criteria

We identified all liver resections in the 5-year period from 1 January 2012 to 31 December 2016. Operations were identified from the Nordic Medico-Statistical Committee (NOMESCO) classification of Surgical Procedures (NCSP), version 2014 [18]. The codes were JJB01/11/21/31/41/51/54/61/97 and JJB71 for laparoscopic resections and all other JJB** codes (JJB00–JJB99) for open resections. Liver resections were further subdivided into major or minor resections according to Brisbane 2000 terminology [19], where major indicated three consecutive segments or more and minor anything else. Where another major resection code (e.g. gastric, pancreatic, rectal or colonic) was used on the same day, the liver resection was excluded as a secondary procedure. Thus, liver resections performed synchronous with a colonic resection are not included in this cohort. We further excluded a very few minor resections performed ad-hoc at non-university hospitals; most were assumed to be biopsies wrongly coded as minor resections.

Descriptors and outcomes

The cohort is described by gender, age groups, comorbidity and main diagnosis. Comorbidity was assessed by the Charlson Comorbidity Index (CCI) [20], with the modification described by Quan for administrative data [21], and applied to apply on diagnoses previously submitted to the NPR. Points assigned for "metastatic tumour" or "any malignancy" were removed as these applied to almost all the patients and

therefore would not provide discriminative information. The process variables were access modality (open or laparoscopic surgery) and major versus minor resection. Outcome variables were aggregated length of stay (a-LoS), re-operation rate and 90 days mortality.

Definitions

Surgical access was assigned as open unless a designated code for laparoscopic resection was used. There are no specific codes in the NCSP denoting conversion. Where patients had both a laparoscopic and an open access resection code at index surgery, the operation was grouped as open.

a-LoS is the sum of postoperative nights in hospital during index stay and any transfer- or readmission stays within 30 days as described in detail elsewhere [17].

Any subsequent laparotomy or laparoscopy codes applied between 1 day and 30 days from index procedure at any hospital in the country was defined as a re-operation. Because of inability to differentiate between a reoperation and several resections on the same day as index procedure, we did not attempt to capture reoperations on the same day as index surgery.

Statistics

Data were analysed using SAS 9.4 (SAS Institute, Cary NC) and Statistical Package for Social Sciences (IBM SPSS, v. 25) and reported as medians, inter-quartile ranges (IQR) and ratios (%) and, where applicable, analysed by non-parametric tests for continuous variables or by Chi-square or Fischer's exact test for rates. Univariate risk analysis and multivariable logistic regression models of all outcomes were created when appropriate, and risk reported as odds ratio (OR) with 95% CI and p value with statistical significance level at 0.050. We have chosen a forward selection strategy for the multivariable models, including covariates according to the p values from the univariable models (lowest p values first). Improvement of the model has been tested by likelihood ratio test at 5% significance level. The models have also been tested for interactions.

Results

A total of 2547 liver resections were reported in the five university centres in Norway over a 5-year period. Some 429 of these were excluded, mainly as being minor parts of other organ resections, leaving a net number of 2118 dedicated liver resections (Fig. 1). Of these, 605 (28.6%) were major and 1513 were minor. Median age was 65 years and 1176 (55%) were males (Table 1). Population-based national incidence rate of resections was 8.3/100.000 inhabitants/year (95% CI

7.9–8.6), and rates in the four regional health authorities varied from 7.5 to 8.7 when corrected for gender and age composition.

Indications

The indications were primary liver or biliary malignancy in 328 patients (15.5%), and of these, 169 (51.5%) were male and 172 (52.4%) had a major resection (Fig. 1). Another 1554 (73.4%) were operated for metastatic disease, and of these, 929 (59.8%) were male and 383 (24.2%) had a major resection (Fig. 1). The remaining 236 (11.1%) patients had unconfirmed malignancy or no malignant disease (Fig. 1). Demographic characteristics are presented in Table 1.

Access modality

Laparoscopic resection was performed in 37 (6.1%) of the patients undergoing major resections, with an increasing rate from 0 to 8% in the 5-year period. In minor resections, laparoscopy was employed in 513 (33.9%) of the patients with a rate increasing from 35.8 to 39.1% in the period. The rate of laparoscopy in minor resections differed between 10.0 and 46.1% in the four regional health authorities.

Length of stay

a-LoS was median 3 days for laparoscopic and 8 days for open minor resections and varied little with age groups (Fig. 2). For major liver resections, the median a-LoS was 12 days for open cases and 5 days for laparoscopic. Almost all the laparoscopic major resections were performed in one centre, and the number is limited ($n = 37$), so further stratification is not attempted.
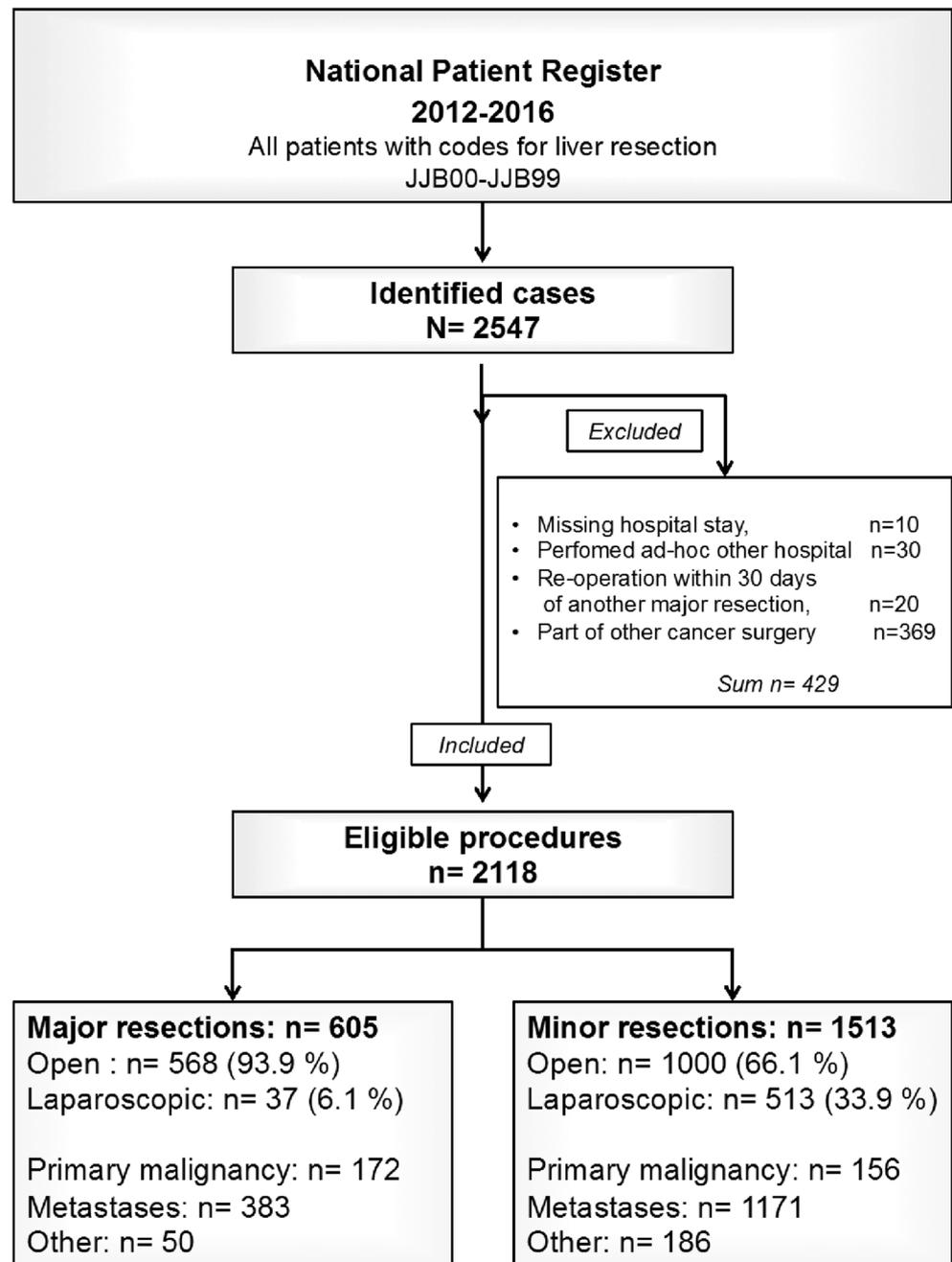
Reoperations

A reoperation was performed in 69 patients (11.4%) after major resections and more frequently in men (13.9% versus 8.2% for women, OR 1.8, 95% CI 1.1–3.2, $p = 0.029$) (Table 2). The reoperation rate after major resection for metastases was 12.8% (49/383) and for resection for primary malignancy, 10.5% (18/172). In patients ≥ 75 years, reoperation rates following major resections were 10.0% (8/80), 16.3% for men and 2.7% for women ($p = 0.044$). Reoperation rates were similar after open minor and laparoscopic minor resections ($p = 0.702$). In multivariable analysis, reoperations were associated with age group 65–74 years, male gender and major resections (Table 2).

Mortality

Mortality at 90 days was 2.1% ($n = 44$) overall and 4.4% (15/345) in patients ≥ 75 years. Following major resections, mortality was 4.3% (26/605) overall, 6.2% (21/337) for men and

Fig. 1 Flowchart

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┌─────────────────────────────────────────────┐
│           National Patient Register          │
│                  2012-2016                    │
│     All patients with codes for liver resection │
│                 JJB00-JJB99                   │
└─────────────────────────────────────────────┘
                      │
                      ▼
          ┌───────────────────────────┐
          │       Identified cases     │
          │          N= 2547           │
          └───────────────────────────┘
                      │
                      │        ┌──────────┐
                      │        │ Excluded │
                      │        └──────────┘
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                      │             ▼
          ┌────────────────────────────────────────────────┐
          │  • Missing hospital stay,            n=10        │
          │  • Perfomed ad-hoc other hospital    n=30        │
          │  • Re-operation within 30 days                   │
          │     of another major resection,      n=20        │
          │  • Part of other cancer surgery      n=369       │
          │                                                  │
          │                          Sum n= 429              │
          └────────────────────────────────────────────────┘
                      │
              ┌──────────┐
              │ Included │
              └──────────┘
                      │
                      ▼
          ┌───────────────────────────┐
          │     Eligible procedures    │
          │          n= 2118           │
          └───────────────────────────┘
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Major resections: n= 605	Minor resections: n= 1513
Open : n= 568 (93.9 %)	Open: n= 1000 (66.1 %)
Laparoscopic: n= 37 (6.1 %)	Laparoscopic: n= 513 (33.9 %)
Primary malignancy: n= 172	Primary malignancy: n= 156
Metastases: n= 383	Metastases: n= 1171
Other: n= 50	Other: n= 186

1.9% (5/268) for women (OR 3.5, 95% CI 1.4–10.6, $p =$ 0.013). Patients undergoing major liver resection for metastatic disease had a 3.1% mortality rate (12/383), with no obvious difference between genders (men $8/233 = 3.4\%$ and women $4/150 = 2.7\%$). Contrary, 172 patients undergoing major liver resection for a primary malignancy (gallbladder $n = 6$, bile ducts $n = 95$, hepatocellular carcinoma $n = 55$, other cancers $n = 16$) had a 7.6% mortality rate (13/172). In multivariable analysis, mortality was associated with advanced age, male gender, CCI > 0, resection for primary malignancy and major resection (Table 3).

Discussion

In this national cohort, overall rates of reoperations (7.5%) and 90-day mortality (2.1%) compare favourably with other population-based series [1, 22, 23]. Major resections, resections for primary liver malignancy, advanced age and male gender were associated with worse outcome. Almost 40% of the minor liver resections were performed by laparoscopy at the end of the period, and this was associated with a considerably shorter length of stay. Laparoscopy for major liver resections is not widely implemented.

Table 1 Characteristics of patients and operations

		Number	Percent
Age (years) Median (IQR)	65 (57–72)		
	< 65	986	46.6
	65–74 years	787	37.2
	75+ years	345	16.3
Male gender		1176	(55.5)
Charlson Comorbidity Index Median (IQR)	0 (0–1)		
	CCI < 1	1552	73.3
	CCI = 1	394	18.6
	CCI > 1	172	8.1
Metastatic malignancy		1554	73.4
Primary liver malignancy		328	15.5
Other indication		236	11.1
Access modality	Laparoscopy	550	26.0
	Open	1568	74.0
Minor resections		1513	71.4
Major resections		605	28.6

A complete national cohort analysis is unsuited to evaluate cause-and-effect relationships, but it is well suited to measure magnitude of effect [11]. Further, it may avoid some of the potential shortcomings of certain randomised trials where the frailest and most comorbid patients may be under-represented [10, 11]. In addition, there is a potential bias in data from single-centre publications, as series with sub-optimal results may remain unpublished. The current study includes all liver resections captured by the NPR (> 2100 resections) from 5 university hospitals over a 5-year period. All patients are covered by a universal healthcare coverage, so inclusion is complete and not skewed by private institutions or insurer selection.
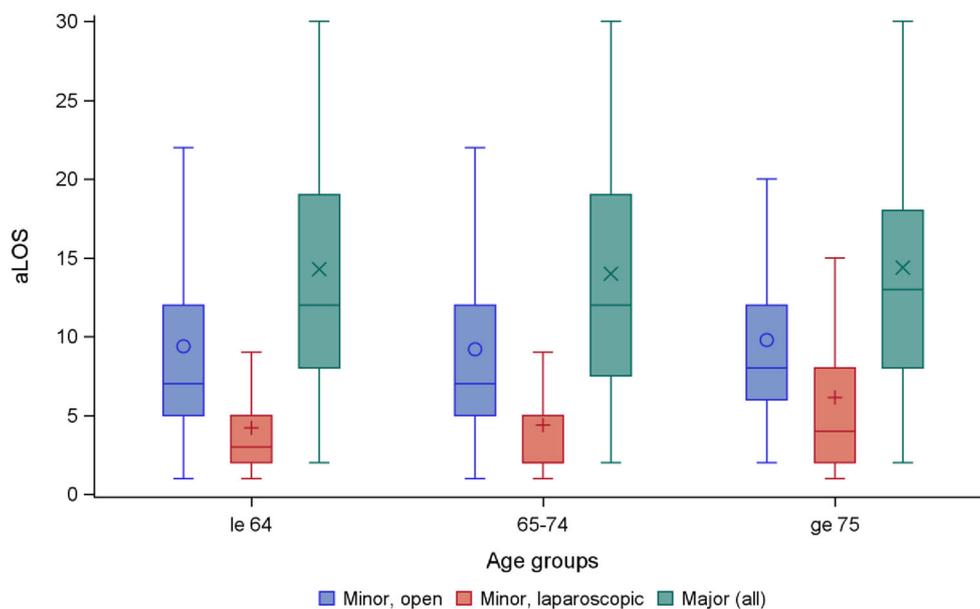
Fig. 2 Box plot of aggregated length of stay (a-LoS) for laparoscopic and open liver resections. Boxes show inter-quartile range (IQR: Q3–Q1). Horizontal lines within boxes are medians (Q2) (Q1 = Q2 for minor laparoscopic in the 65–70 age group). Means are marked by "circle", "plus sign" and "multiplication sign" for minor open, minor laparoscopic and major resections respectively. Upper whisker fence is Q3 + (IQR × 1.5). Lower whisker fence is the lowermost value within Q1 − (IQR × 1.5). Note that stays are truncated at 30 days and hence means are skewed. Due to the small number of laparoscopic major resections ($n = 37$), the major group is shown as one with all cases irrespective of access.

Table 2 Risk factors for reoperation at 30 days after surgery

	No. of patients, n (%)	Relaparotomy, n (%)	Univariable odds ratio (95% CI)	Multivariable odds ratio* (95% CI)
All	2118	159 (7.5)		
Age group			$p = 0.090$	Not included
≤ 64	986 (46.6)	87 (8.8)	Ref	
65–74	787 (37.2)	48 (6.1)	0.67 (0.46–0.96)	
≥ 75	345 (16.3)	24 (7.0)	0.77 (0.47–1.22)	
Gender			$p = 0.024$	$p = 0.024$
Female	942 (44.5)	57 (6.1)	Ref	Ref
Male	1176 (55.5)	102 (8.7)	1.47 (1.06–2.08)	1.47 (1.06–2.08)
CCI			$p = 0.939$	Not included
< 1	1552 (73.3)	115 (7.4)	Ref	
1	394 (18.6)	30 (7.6)	1.03 (0.67–1.54)	
≥ 2	172 (8.1)	14 (8.1)	1.11 (0.60–1.91)	
Indication			$p = 0.091$	Not included
Metastatic liver tumour	1554 (73.4)	119 (7.7)	Ref	
Primary malignancy	328 (15.5)	30 (9.1)	1.21 (0.79–1.82)	
Other	236 (11.1)	10 (4.2)	0.53 (0.26–1.98)	
Access			$p = 0.238$	Not included
Laparoscopic	550 (26.0)	35 (6.4)	Ref	
Open	1568 (74.0)	124 (7.9)	1.26 (0.87–1.89)	
Resection			$p = <0.001$	$p = <0.001$
Minor	1513 (71.4)	90 (5.9)	Ref	Ref
Major	605 (28.6)	69 (11.4)	2.04 (1.46–2.82)	2.04 (1.46–2.83)

*Factors included in multivariable logistic regression: gender and resection type

Two recent reports from the American College of Surgeons' National Surgical Quality Improvement Program (ACS-NSQIP) included all registered liver resections for 2014, totalling just short of 2900 patients from 92 hospitals [24], among which 65 were high-volume medical centres [6]. While the present cohort is smaller, it includes all patients operated in the country and as such present an unbiased real-life illustration of short-term outcomes in the modern era of liver surgery. Importantly, mortality is reported here at 90 days, in line with several reports warning that 90-day mortality is two to three times higher than 30-day or in-house mortality [1, 25].

The national incidence of liver resections at 8.3 per 100,000 inhabitants per year is in line with previous reports from Scandinavia, where, e.g. Sweden had a resection rate of 8.1 for the year 2011 [1]. The five Norwegian hospitals providing liver surgery are all university hospitals, which have been shown to be associated with improved outcomes for both primary and secondary liver tumours [26, 27].

Laparoscopic access was employed by all hospitals for minor resections albeit to a different degree (hospital data not shown). Laparoscopy was associated with shorter a-LoS compared to open resection. The difference in days for minor resections (median 3 vs. 8) is substantially larger than what has been shown in a recent randomised trial from Norway, where the corresponding numbers were 2 and 4 days, for laparoscopic and open minor resections, respectively [28]. Apart from some trial (Hawthorne) effect, this probably implies that there is a selection bias in a non-trial setting, favouring smaller or easier resections in healthier patients for laparoscopy. It may, however, also suggest that perioperative care for patients having open surgery may be further improved with a resultant shorter length of stay. The use of a-LoS, in place of conventional index LoS, implies the incorporation of both transfer and readmission stays within 30 days from surgery and is a more comprehensive illustration of healthcare utilisation [17]. Laparoscopy has previously been shown to be associated with fewer complications [9, 28], but it was not associated with lower major morbidity or mortality in this cohort. The number of major resections performed laparoscopically was too small to make any stratified conclusions, but a significant association with shorter a-LoS was shown.

Centralization and higher volumes have repeatedly been shown to be associated with improved outcomes [23, 29–31]. The cut-offs chosen for low and high volume centres, however, varied considerably [22, 29, 30]. Yearly case-load numbers of 11 [29], 20 [22] and 43 [30] have all been used to define high-volume hospitals. All five Norwegian centres had

Table 3 Risk factors for mortality at 90 days after surgery

	No. of patients, n (%)	Mortality, n (%)	Univariable odds ratio (95% CI)	Multivariable odds ratio* (95% CI)
All	2118	44 (2.1)		
Age group			p = 0.005	p = 0.006
≤ 64	986 (46.6)	13 (1.3)	Ref	Ref
65–74	787 (37.2)	16 (2.0)	1.55 (0.74–3.31)	1.41 (0.67–3.03)
≥ 75	345 (16.3)	15 (4.3)	3.40 (1.60–7.33)	3.43 (1.57–7.59)
Gender			p = 0.011	p = 0.014
Female	942 (44.5)	11 (1.2)	Ref	Ref
Male	1176 (55.5)	33 (2.8)	2.44 (1.27–5.09)	2.44 (1.24–5.17)
CCI			p = 0.003	p = 0.042
< 1	1552 (73.3)	22 (1.4)	Ref	Ref
1	394 (18.6)	14 (3.6)	2.56 (1.27–5.00)	2.09 (1.02–4.17)
> 1	172 (8.1)	8 (4.7)	3.39 (1.40–7.45)	2.44 (0.97–5.59)
Indication			p = <0.001	p = 0.019
Metastatic liver tumour	1554 (73.4)	23 (1.5)	Ref	Ref
Primary malignancy	328 (15.5)	18 (5.5)	3.87 (2.04–7.23)	2.59 (1.31–5.04)
Other	236 (11.1)	3 (1.3)	0.86 (0.20–2.49)	1.22 (0.28–3.69)
Access			p = 0.032	Not included
Laparoscopic	550 (26.0)	5 (0.9)	Ref	
Open	1568 (74.0)	39 (2.5)	2.78 (1.20–8.10)	
Resection			p = <0.001	p = 0.001
Minor	1513 (71.4)	18 (1.2)	Ref	Ref
Major	605 (28.6)	26 (4.3)	3.73 (2.04–6.96)	3.35 (1.77–6.46)

*Factors included in multivariable logistic regression: age, gender, Charlson comorbidity score (CCI), indication and resection type

a mean yearly volume of > 20 resections in the period and three of them had more than 43 cases per year. A recent publication presented the liver resections in Sweden in the decade preceding our cohort (2002–2011) [1]. Mortality in the Swedish cohort was 1.8% and 3.1% after 30 and 90 days respectively, and a total of 40 hospitals performed liver resections throughout the period [1]. Even considering that Sweden's population is almost twice that of Norway's, this is a marked contrast to the five hospitals doing all the liver surgery in Norway and this has been unaltered for more than a decade. That 90-day mortality among the Norwegian patients was even lower overall (2.1%) than in Sweden might result both from a stricter and more long-standing centralization and from a general improvement in selection and technique resulting from being a later cohort than the Swedish one.

The composition of diagnoses in the Norwegian cohort reflects a typical Scandinavian pattern with a relatively low rate of primary liver malignancy (15.5%). This is about half of what is reported in recent series from the USA [2], and it is even lower than in the Swedish cohort (20%) [1]. The 90-day mortality for all resections for metastases (1.5%) is similar to what has been shown as perioperative mortality in a large French series [32]. Resection of a primary tumour as a contrast to a metastatic tumour was associated with increased

morbidity and mortality in our cohort, and this has been shown in several other series [2–5, 33]. Others have shown this to be independent of hepatic dysfunction and extent of resection performed [4], but it has been proposed that some lifestyle characteristics frequently associated with cirrhosis and primary liver cancer may be responsible for poorer outcomes after surgery even in non-cirrhotic patients [4]. In major liver resections, the mortality for primary malignancies was more than twice that of metastatic disease (7.6 versus 3.1%) and following minor resections it was more than three times higher (3.2 versus 0.9%). The mortality rate for men following major resection for primary malignancy was especially high at 13.2% compared to 1.2% for women. For metastatic disease, the difference was small (3.4% for men and 2.7% for women). To our knowledge, there is no accepted hypothesis to explain this gender difference.

This study has some limitations. The coding system did differentiate between reoperations performed for different causes, but we have no validation for the quality of this sub-classification and hence have reported all reoperations together. To avoid inclusion of small liver resections as parts of large multi-visceral resections, we excluded resections were other organ resections were performed at the same date. This will have excluded a small number of synchronous resections of

colonic primaries and liver metastases. The rate of conversions from laparoscopic to open access is not possible to estimate from this dataset as there is no designated conversion code. We assume that when conversions were performed very early in the procedure, they might only have an open procedure code. Conversely, a very late conversion may only have a laparoscopic resection code. What can be affirmed is that operations coded as laparoscopy were indeed commenced as laparoscopy and those coded as open were completed as open procedures. Lastly, due to the nature of our dataset, we have no information about liver function, degree of cirrhosis, size or number of tumours.

The strength of the paper is the lack of selection. All patients and all surgeons in all hospitals are included in the cohort, and it shows the magnitude of the various outcomes. As such, it provides a "true" landscape against which one may compare single-centre series and control groups in randomised trials. A "poor control" group is a problem in many trials, and this provides a reference from real life. Our study covers a complete national cohort in a country with a universal healthcare system assuring equal access for all and where liver surgery is centralised to a few university hospitals. While risk factors for unwanted outcomes were in line with previous reports, we were able to quantify the impact across the nation, for all patients and all surgeons. The consistent risk associated with male gender is striking and largely unexplained and deserves further exploration. In the laparoscopic era, "minor" liver resections, according to the Brisbane definition [19], probably need further stratification to correctly predict complexity and risk [34, 35]. Administrative data, especially in single-payer systems with complete cohorts, represent a relevant source for outcomes research where magnitude of effect in the population is under investigation, in line with the framework of the IDEAL recommendations [36].

To conclude, in this complete, national 5-year cohort of hepatectomies, laparoscopy was extensively used and associated with reduced length of stay compared to open. Overall rates of reoperations and mortality were reassuring, with the poorest outcomes in elderly, males, major resections and in resections for primary liver tumours.

Compliance with ethical standards

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