

# Humanistic and Economic Burden of Recurrence in Early-Stage Hepatocellular Carcinoma: Systematic Literature Review

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## Introduction

- Liver cancer is the third-most common cause of cancer-related death globally, with hepatocellular carcinoma (HCC) being the most common type of liver cancer.<sup>1</sup>
- Curative-intent treatments (resection, ablation or liver transplantation) are **preferred** for early-stage HCC.<sup>2,3</sup>
- Despite curative-intent resection/ablation, HCC **recurrence** can occur in **70–90% of cases** within 5 years and is the **major cause of death** after curative-intent treatment.<sup>4–6</sup>
- Although the clinical burden of HCC recurrence has been established, there remains a gap in the understanding of the associated **humanistic and economic burden**.

## Objective

- This systematic literature review (SLR) aimed to identify evidence on the humanistic and economic burden of HCC recurrence following resection or ablation.

## Methods

- For this SLR, **electronic databases** were searched in October 2023 and supplemented by **grey literature** hand searches (performed from November 2023–December 2023; **Figure 1**).

Figure 1. Electronic databases and grey literature sources

Electronic Databases		Grey Literature Sources	
MEDLINE	Embase	11 relevant congresses	HTA body websites
NHS EED	HTAD	Bibliographies*	Targeted searches
Economic websites			

**Footnotes:** \*Bibliographies of all relevant SLRs, network meta-analyses, HTA body websites and economic evaluations were searched.

- Eligible articles reported health-related quality of life (HRQoL) and healthcare resource use (HCRU) data, including treatment patterns, for HCC patients with recurrence following resection/ablation (**Table 1**).
- Costs are reported in US dollars (2019).

Table 1. Eligibility criteria

Domain	Inclusion criteria	
SLR stream	HSUV/HRQoL	HCRU
Patient population	<ul style="list-style-type: none"><li>Adults who received curative ablation and/or resection for early-stage HCC with recurrent disease</li><li>Caregivers of patients with HCC</li></ul>	
Intervention/comparator	Any or none	
Outcomes	<ul style="list-style-type: none"><li>HSUVs, HRQoL and patient reported outcomes, measured using a validated, published instrument</li></ul>	<ul style="list-style-type: none"><li>Treatment patterns</li><li>Direct and indirect resource use</li><li>Direct and indirect costs</li></ul>
Study design	Any primary research reporting novel data	
Publication date	No date restrictions	Articles published in or after 2013
Other	<ul style="list-style-type: none"><li>Abstract or full-text in English</li><li>Studies in humans</li><li>Any geographical location</li></ul>	

## References

1. National Cancer Institute. Liver Cancer Causes, Risk Factors, and Prevention. Available at: [www.cancer.gov/types/liver/what-is-liver-cancer/causes-risk-factors](https://www.cancer.gov/types/liver/what-is-liver-cancer/causes-risk-factors) (Accessed October 2024); 2. ESMO Guidelines Committee. eUpdate – Hepatocellular Carcinoma Treatment Recommendations. Available at: <https://www.esmo.org/guidelines/guidelines-by-topic/esmo-clinical-practice-guidelines-gastrointestinal-cancers/hepatocellular-carcinoma-esmo-clinical-practice-guidelines-for-diagnosis-treatment-and-follow-up/eupdate-hepatocellular-carcinoma-treatment-recommendations> (Accessed September 2024); 3. Omata et al. Hepatol Int. 2017; 11(4):317–370; 4. Kudo. Oncology. 2011;81(Suppl 1):50–55; 5. Bruix and Sherman. Hepatology. 2005;42(5):1208–1236; 6. Zhou et al. BMC Cancer. 2015;15(689); 7. Poon et al. Arch Surg. 2001;136(6):693–699; 8. Tanabe et al. Hepatogastroenterology. 2001;48(38):506–510; 9. Wang et al. Qual Life Res. 2007;16(3):389–397; 10. Xiao et al. Am J Transl Res. 2019;11(3):1864–1875; 11. Cen et al. Front Med (Lausanne). 2023;11(10):1127122; 12. Ding et al. Sci Rep. 2017;14(7):44583; 13. Zhang et al. Chin J Cancer. 2016;8(35):25; 14. Imai et al. Hepatol Res. 2014;44(14):E335–345; 15. Terashima et al. Hepatol Res. 2021;51(10):1073–1081; 16. Ektare et al. Value in Health. 2022;25(7):S379.

## Plain Language Summary

### Why did we perform this research?

- Hepatocellular carcinoma (HCC) is a type of liver cancer that can return (termed recurrence), even if patients receive treatments that aim to cure the cancer (e.g., ablation or resection).
- Patients who experience recurrence have worse survival outcomes than those who don't experience recurrence.
- This study aimed to better understand the impact of recurrence, in terms of patient quality of life and costs.

### How did we perform this research?

- We searched for evidence from patients who experienced HCC recurrence following ablation or resection, looking for:
  - Patient quality of life after HCC recurrence.
  - The type of treatments patients receive for recurrence.
  - The costs associated with these treatments and disease management.

### What were the findings of this research?

- HCC recurrence negatively impacts patients' quality of life.
- Most patients with HCC recurrence receive treatment, and these treatments are associated with substantial costs.

### What are the implications of this research?

- There is a high unmet need for therapies that reduce the risk of recurrence in patients who have received resection or ablation for HCC. These treatments would alleviate the negative impact of recurrence on patient quality of life and reduce the costs associated with recurrence.

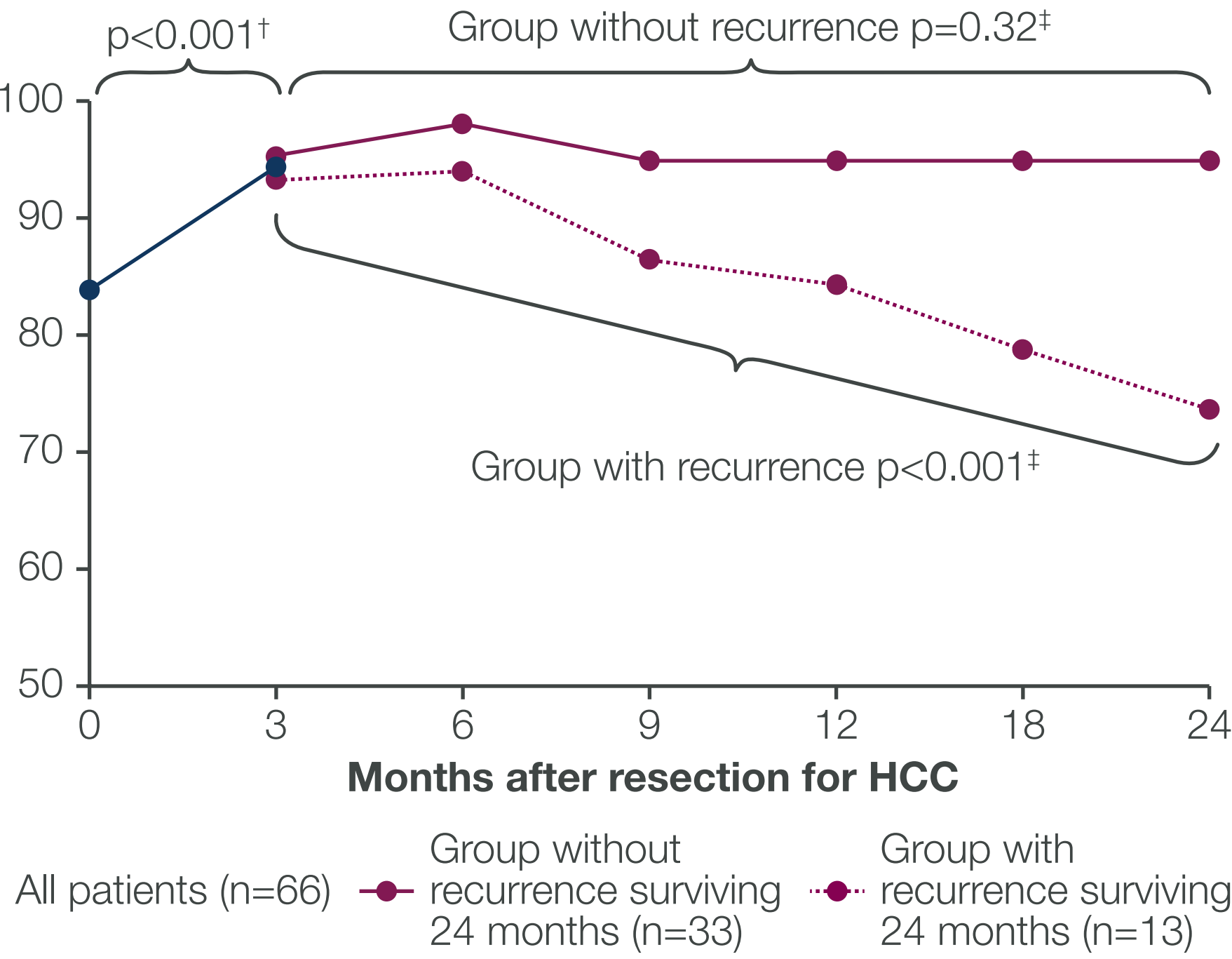
## Results

- Of the 1,381 database and 4,770 grey literature records screened, 34 publications reporting HRQoL (n=3), treatment pattern (n=25) and HCRU (n=12) data were included.

### HRQoL (n=3)

- All studies were conducted in East Asia, with data collected ≥20 years ago, small sample sizes and limited reporting of baseline characteristics.
- From the limited evidence, resection improved HRQoL (measured using FACT-G) versus before treatment (p<0.001 [blue line; **Figure 2**]).<sup>7</sup>
- Patients with recurrence had:
  - Lower FACT-G (p<0.001 [pink lines; Figure 2]) and ECOG-PS (16/28 patients) versus post-initial treatment.<sup>7,8</sup>
  - Lower FACT-G versus those who remained recurrence free (p<0.05).<sup>9</sup>

Figure 2. Summary of FACT-G score following resection of HCC in Poon 2001<sup>7</sup>



**Footnotes:** Figure adapted from Poon 2001<sup>7</sup>; <sup>†</sup>Versus preoperative FACT-G total score; <sup>‡</sup>Versus 3-month postoperative FACT-G total score.

### Treatment patterns (n=25)

- Few studies reflected recent treatment patterns, with only 3/25 studies exclusively collecting data after 2014; data were primarily collected in Asia.
- Of studies reporting treatment patterns, 21/25 reported treatments for first recurrence.
- The range of utilisation across studies was very wide, likely reflecting different patient and tumour characteristics, such as whether recurrence was intra- or extrahepatic.
- The most frequently reported treatments for first recurrence were ablation (n=14), embolisation (n=13) and resection (n=13; **Table 2**).
- Systemic therapies and liver transplantation were less frequently reported, with donor shortage mentioned as a key reason for the latter (**Table 2**).
- Fewer studies reported supportive/palliative therapy or no treatment (**Table 2**), indicating most patients receive active HCC treatment for first recurrence.

Table 2. Range of the proportion of patients receiving HCC treatment for first recurrence

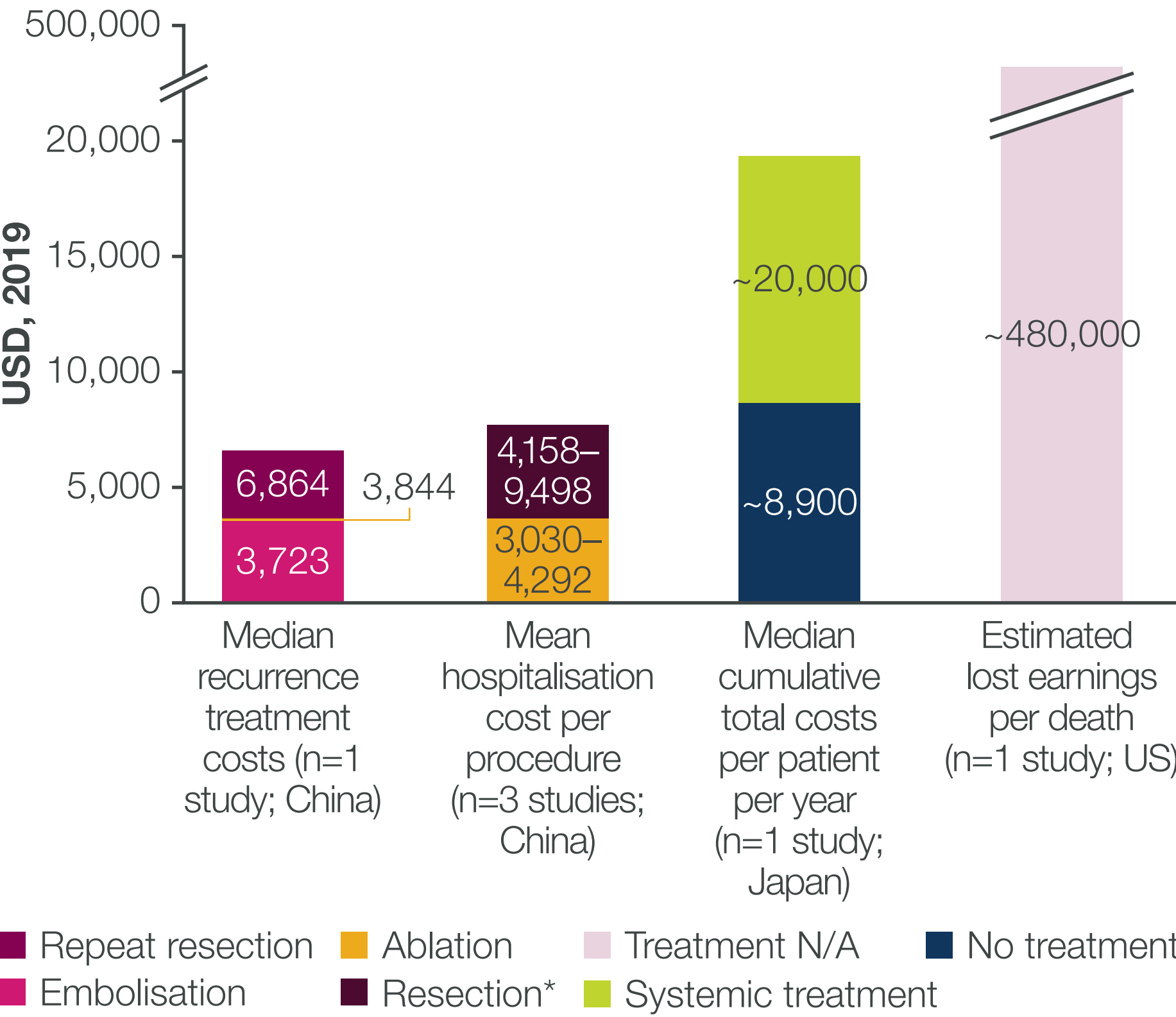
Treatment	Number of studies	Patients receiving treatment (%)
Ablation	14	1.5–80.0
Embolisation	13	1.5–69.7
Resection	13	0.0–39.9
Resection or ablation	1	26.8–34.8
Systemic therapy*	10	0.0–63.6
Liver transplantation	7	0.0–42.9
Radiotherapy	3	0.0–23.4
Hepatic arterial infusion	1	43.8–68.5
Locoregional therapy**	1	26.8–40.7
Supportive/palliative therapy	5	1.2–25.4
No treatment	3	7.0–14.6

**Footnotes:** \*Includes chemotherapy, molecular targeted agents/sorafenib and unspecified treatment; \*\*Details of treatment not further specified.

### HCRU and Costs (n=12)

- Few studies reported recent HCRU and cost data; data were primarily collected in Asia.
- The cost of resection to treat recurrence was substantially higher than ablation or embolisation (**Figure 3**).
  - Median recurrence treatment costs: \$6,864 for repeat resection, \$3,844 for ablation and \$3,723 for embolisation.<sup>10</sup>
  - Mean hospitalisation cost per procedure: \$4,158–9,498 for resection and \$3,030–4,292 for ablation (no data for embolisation available).<sup>11–13</sup>
- Mean length of hospital stay was longer for resection versus ablation (resection: 6.5–22.1 days; ablation: 2.8–10.5 days).<sup>11,12,14</sup>
- Patients receiving no active treatment still incurred substantial cumulative total costs (**Figure 3**).<sup>15</sup>
- Indirect costs estimated that ~\$0.5 million in earnings are lost per death due to HCC recurrence in the United States (**Figure 3**).<sup>16</sup>

Figure 3. Summary of direct and indirect costs associated with HCC recurrence



**Footnotes:** Where a range is reported, bars show mean reported costs; \*One study reported repeat resection, two studies reported resection.

## Conclusions

- Based on limited evidence, patients with recurrent HCC have reduced and deteriorating HRQoL, compared with patients who remain recurrence-free after treatment.
- Most patients with recurrent HCC receive active treatment and recurrence is associated with a substantial economic burden.
- There is an unmet need for treatments that reduce the risk of recurrence and its burden by preserving the HRQoL improvements achieved by initial treatment and avoiding the need for further treatment or disease management.
- Further, more recent studies are required to understand the humanistic and economic burden of recurrence, particularly in Western countries.

## Abbreviations

**ECOG-PS**, Eastern Cooperative Oncology Group Performance Status; **FACT-G**, Functional Assessment of Cancer Therapy–General; **HCC**, hepatocellular carcinoma; **HCRU**, healthcare resource use; **HRQoL**, health-related quality of life; **HSUV**, health state utility value; **HTA**, health technology assessment; **HTAD**, Health Technology Assessment Database; **N/A**, not applicable; **NHS EED**, National Health Service Economic Evaluation Database; **SLR**, systematic literature review; **US**, United States; **USD**, United States Dollar.

## Funding

This study was funded by AstraZeneca.

## Acknowledgements

The authors thank Costello Medical for editorial assistance and publication coordination, on behalf of AstraZeneca, and acknowledge Hannah Russell, Costello Medical, UK for medical writing and editorial assistance based on authors' input and direction.

## Disclosures

**VP, JS, RP:** employees and stockowners of AstraZeneca; **EW, AK, ED:** consulting fees from AstraZeneca (paid to Costello Medical) and employees of Costello Medical.