

ORIGINAL ARTICLE

# Heterogeneity of management practices surrounding operable gallbladder cancer – results of the OMEGA-S international HPB surgical survey

Anita Balakrishnan<sup>1</sup>, Asif Jah<sup>1</sup>, Mickael Lesurtel<sup>2</sup>, Bodil Andersson<sup>3</sup>, Paul Gibbs<sup>1</sup>, Simon J.F. Harper<sup>1</sup>, Emmanuel L. Huguet<sup>1</sup>, Vasilis Kosmoliaptis<sup>1</sup>, Siong S. Liau<sup>1</sup>, Raaj K. Praseedom<sup>1</sup>, Jose M. Ramia<sup>4</sup>, Alejandro Branes<sup>5</sup>, Javier Lendoire<sup>6</sup>, Shishir Maithe<sup>7</sup>, Alejandro Serrablo<sup>8</sup>, The EAHPBA Scientific and Research Committee and the OMEGA study collaborators<sup>1</sup>

<sup>1</sup>Department of HPB Surgery, Cambridge University Hospitals NHS Foundation Trust, Hills Road, Cambridge, CB2 0QQ, United Kingdom, <sup>2</sup>Department of HPB Surgery and Liver Transplantation, Beaujon Hospital, University of Paris Cité, 100 Bd du Général Leclerc, 92110, Clichy, France, <sup>3</sup>Department of Surgery, Lund University, Skane University Hospital, Lund, Sweden, <sup>4</sup>Department of Surgery, Hospital General Universitario de Alicante, Avenida Pintor Baeza, 12 03010 Alicante, Spain, <sup>5</sup>Department of HPB Surgery, Hospital Sotero del Rio, Av. Concha y Toro 3459, Puente Alto, Región Metropolitana, Chile, <sup>6</sup>Department of Surgery, University of Buenos Aires, Hospital Dr Cosme Argerich, Buenos Aires, Argentina, <sup>7</sup>Department of Surgery, Emory University School of Medicine, Atlanta, GA, 30322 USA, and <sup>8</sup>Department of HPB Surgery, Miguel Servet University Hospital, Zaragoza, Spain

## Abstract

**Background:** Gallbladder cancer (GBC) is an aggressive, uncommon malignancy, with variation in operative approaches adopted across centres and few large-scale studies to guide practice. We aimed to identify the extent of heterogeneity in GBC internationally to better inform the need for future multi-centre studies.

**Methods:** A 34-question online survey was disseminated to members of the European-African Hepatopancreatobiliary Association (EAHPBA), American Hepatopancreatobiliary Association (AHPBA) and Asia-Pacific Hepatopancreatobiliary Association (A-HPBA) regarding practices around diagnostic workup, operative approach, utilization of neoadjuvant and adjuvant therapies and surveillance strategies.

**Results:** Two hundred and three surgeons responded from 51 countries. High liver resection volume units (>50 resections/year) organised HPB multidisciplinary team discussion of GBCs more commonly than those with low volumes ( $p < 0.0001$ ). Management practices exhibited areas of heterogeneity, particularly around operative extent. Contrary to consensus guidelines, anatomical liver resections were favoured over non-anatomical resections for T3 tumours and above, lymphadenectomy extent was lower than recommended, and a minority of respondents still routinely excised the common bile duct or port sites.

**Conclusion:** Our findings suggest some similarities in the management of GBC internationally, but also specific areas of practice which differed from published guidelines. Transcontinental collaborative studies on GBC are necessary to establish evidence-based practice to minimise variation and optimise outcomes.

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## Correspondence

Anita Balakrishnan, Department of HPB Surgery, Cambridge University Hospitals NHS Foundation Trust, Hills Road, Cambridge, CB2 0QQ, United Kingdom. E-mail: [anita.balakrishnan@doctors.org.uk](mailto:anita.balakrishnan@doctors.org.uk)

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<sup>1</sup> Members of the OMEGA-S Collaborative Study Group are co-authors of this study and listed in the 'Collaborators' section.

## Introduction

Gallbladder cancer (GBC) remains a condition with a poor prognosis, with an average five-year survival ranging between 5 and 15%.<sup>1,2</sup> GBC may be diagnosed either pre-operatively based on radiographic imaging, or discovered incidentally during surgery or on histological analysis following cholecystectomy for presumed benign disease.<sup>2</sup> Adequate staging and pre-operative workup, as well as careful consideration of operative approach and extent, are essential in ensuring optimal outcomes from for patients with GBC.

The relatively infrequency of this diagnosis in most countries has resulted in few large-scale studies to establish best practices, and hence staging, operative approach and post-operative management often differ within and between countries.<sup>3</sup> There remains some debate in the literature regarding the extent of liver resection and lymphadenectomy necessary for various stages of GBC, as well as the need for re-resection for early stages of incidental GBC.<sup>4–6</sup> Consensus statements have been written by several hepatopancreatobiliary surgical associations internationally based on currently available evidence to guide decision-making, however there has been little global assessment of how consistently these guidelines or the recommendations from the published literature are followed.<sup>1,7–9</sup>

This study aimed to assess surgical practice regarding the management of GBC, as well as the views of the international community of Hepato-Pancreato-Biliary (HPB) surgeons on the factors influencing resectability, surgical approaches and peri-operative management of GBC, to identify areas of heterogeneity of practice and thus avenues for future studies.

## Methods

A survey questionnaire was designed by the members of the Scientific and Research Committee of the European-African Hepatopancreatobiliary Association (EAHPBA) to assess practice patterns in diagnostic workup, operative approach, utilization of neoadjuvant and adjuvant therapies and surveillance strategies across centres and countries. Respondents were also asked about the annual case volume of gallbladder cancers in their units as well as annual overall liver resection volume.

The survey consisted of 34 questions with specific options for either single or multiple answers and was designed to be completed within approximately 25 min (see Supplementary Material).

Invitations to respond to the survey were sent out via email to members of the EAHPBA, American Hepatopancreatobiliary Association (AHPBA) and Asia-Pacific Hepatopancreatobiliary Association (A-HPBA), with a reminder sent out after three weeks of the initial correspondence.

In accordance with the NHS Health Research Authority questionnaire, no ethical approval was required for this study.

Data analysis and figure design was performed using Graph-Pad Prism® (San Diego, CA, USA). Responses were described as

counts and percentages for categorical variables and statistical analyses of categorical data, where appropriate, were performed with the Chi-square test or Fisher's exact test.  $p < 0.05$  was considered to meet statistical significance.

## Results

### Demographics of responders

Two hundred and three HPB surgeons responded to the survey from a total of 51 countries, with 61.6% and 36.8% of respondents working in units performing over 50 and 100 liver resections per year respectively. Approximately half of the respondents (52.7%) worked in units performing between 5 and 15 gallbladder cancer resections per year while only five respondents (2.5%) reported more than 50 gallbladder cancer resections per year. EAHPBA members formed 64.0% of survey respondents, while 10.8% and 25.1% were from the AHPBA and A-HPBA respectively. The proportion of respondents from each HPB association working in high volume centres (defined as centres performing more than 50 liver resections per year) was 69.2%, 54.5% and 51.0% from the EAHPBA, AHPBA and A-HPBA respectively.

### Staging and decision-making

Routine discussion of all GBCs in a HPB multidisciplinary team (MDT) was reported by 137 respondents (67.5%), while 44 (21.7%) discussed these cases in a general cancer MDT. Twenty-two respondents (10.8%) reported no formal MDT discussion of GBCs in their units. Discussion at a HPB MDT was more likely to take place at centres with an annual volume of 50 or more liver resections compared to centres with lower resection volumes ( $p < 0.0001$ ).

Usage of pre-operative staging modalities was similar after incidentally discovered GBC and pre-operatively detected GBC, although Positron Emission Tomography and Computed Tomography (PET CT) scanning was more commonly used in the evaluation for further surgery in incidental gallbladder cancer (Table 1). Staging of pre-operatively suspected GBC was more likely to be performed with Magnetic Resonance Imaging (MRI) and PET CT in units with liver resection volumes of more than 50 cases per year (Table 1,  $p = 0.185$  and  $0.099$  respectively), and with staging laparoscopy in units with liver resection volumes of less than 50 cases per year ( $p = 0.103$ ). This difference in the reported utilisation of staging modalities between high and low volume liver resection units was also similarly noted for staging of incidentally discovered GBC, with significantly more low resection volume units performing staging laparoscopy for these cases compared to high resection volume units (Table 1,  $p = 0.011$ ).

Biopsy-proven involvement of the coeliac, superior mesenteric or para-aortic lymph nodes was considered an absolute contra-indication to resection by 173 (86.9%) of respondents (Table 2). This number dropped to 50.3% if involvement of these nodes was only suspected on imaging rather than confirmed. 26.1% of

respondents felt that biopsy-confirmed involvement of the peripancreatic or common hepatic artery nodes would be a contraindication to surgery. 47.7% of respondents stated they would proceed to resection despite the presence of a solitary right-sided liver metastasis.

### Operative approach and extent of resection

Most respondents performed a simple cholecystectomy laparoscopically (159 respondents, 78.3%) whether for incidental or pre-operatively diagnosed GBC, however more than 53% of respondents used an open rather than laparoscopic or robotic approach when cholecystectomy was combined with an anatomical liver resection, lymphadenectomy or hepaticojejunostomy. The type of liver resection reported for individual tumour stages varied, in particular for stages T2a and T2b, but broadly increased in extent with increasing stage of tumour (Fig. 1). Cholecystectomy alone was the most favoured option for management of T1a tumours (80.7% of responses). Wedge (non-anatomical) resections were favoured for T1b and T2a tumours (69.1% and 60.7% of responses respectively), and anatomical segment IVb/V resections were favoured for T2b and T3 tumours (51.4% and 50.8% of responses respectively). Wedge (non-anatomical) resection was uncommonly considered for tumours at stage T3 and above (12.5% of responses).

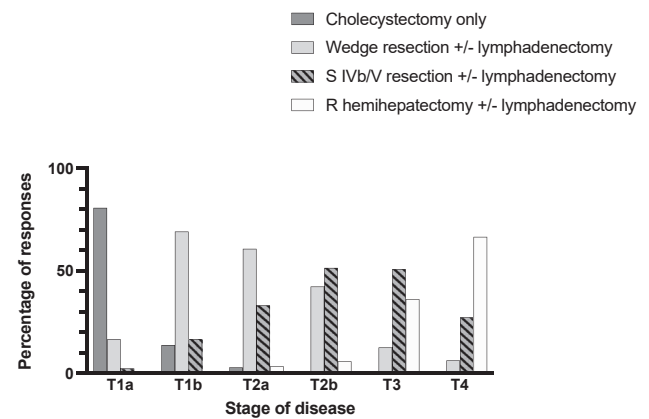
The extent of liver resection performed at the time of resection for incidental GBC was broadly similar to that for pre-operatively diagnosed GBC. Most respondents would not perform further surgery for incidental T1a tumours but would re-intervene to perform liver resection for incidental T1b tumours and above (Fig. 2). Wedge (non-anatomical) resections were considered sufficient for T1b and T2a tumours (64% and 63.5% of responses respectively), while segment IVb/V resection was the most common choice of operative intervention for T2b and T3 tumours (54.2% and 69.4% of responses respectively).

Hilar lymphadenectomy was routinely performed by 66% of respondents for T1b tumours and by 73.4% and 90.6% of

**Table 2** Perceived absolute contraindications to resection of GBC

Criteria considered absolute contraindications to resection	Number of respondents (percentage)
Biopsy-proven para-aortic, coeliac or SMA nodes	173 (86.9%)
Main PV involvement	115 (57.8%)
Solitary right-sided liver metastasis	104 (52.3%)
Suspected involvement of paraaortic, coeliac or SMA nodes	100 (50.3%)
Colon/stomach/duodenum involvement	55 (27.6%)
Biopsy-proven CHA or peripancreatic node involvement	52 (26.1%)
Jaundice at presentation (hilar compression)	37 (18.6%)
Suspected involvement of CHA or peripancreatic nodes	22 (11.1%)

SMA, superior mesenteric artery; PV, porta vein; CHA, common hepatic artery.

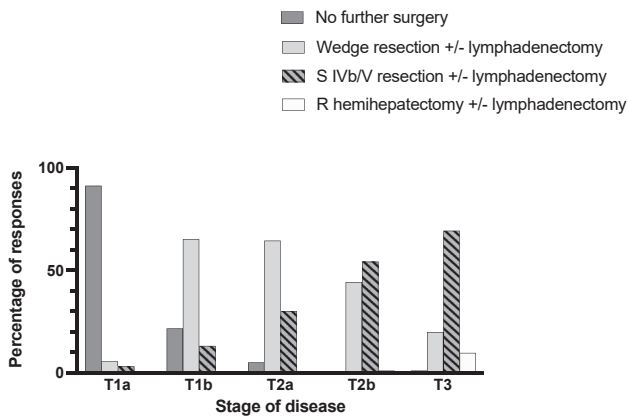


**Figure 1** Extent of liver resection for pre-operatively diagnosed gallbladder cancer. The percentage of responses selecting the various options is shown on the y-axis, and the T-stages on the x-axis

**Table 1** Modalities employed in the pre-operative investigation of GBC

	Low liver resection rate (<50 per year)	High liver resection rate (>50 per year)	All units	p-value
<b>Pre-operatively suspected GBC</b>				
CT	73 (93.6%)	119 (95.2%)	192 (94.6%)	0.752
MRI	42 (53.8%)	80 (64.0%)	122 (60.1%)	0.1850
PET CT	10 (12.8%)	28 (22.4%)	38 (18.7%)	0.099
Staging lap	26 (33.3%)	28 (22.4%)	54 (26.6%)	0.103
<b>Staging following incidental GBC</b>				
CT	66 (84.6%)	112 (89.6%)	178 (87.7%)	0.380
MRI	42 (53.8%)	65 (52.0%)	107 (52.7%)	0.885
PET CT	23 (29.5%)	47 (37.6%)	70 (34.5%)	0.288
Staging lap	32 (41.0%)	29 (23.2%)	61 (30.0%)	0.011*

GBC, gallbladder cancer; CT, computed tomography; MRI, magnetic resonance imaging; PET CT, positron emission tomography and computed tomography. Statistical significance was calculated using the Fisher's test.



**Figure 2** Extent of liver resection performed at re-operation for incidental gallbladder cancer. The percentage of responses selecting the various options is shown on the y-axis, and the T-stages on the x-axis

respondents for stages T2 and above respectively (Fig. 3). In comparison, peripancreatic and common hepatic artery nodes were removed less frequently, particularly for earlier stages of disease (by up to 45.8% of respondents for T1b tumours and up to 71.9% of respondents for T4 tumours). Para-aortic nodes were routinely removed by 5% of respondents for T1b tumours and by 24% of respondents for T4 tumours.

Routine resection of the common bile duct (CBD) was rarely performed for stages T1 and T2 disease (up to 7.4% of respondents), but always carried out by 21% and 31% of respondents for T3 and T4 tumours respectively. Port site resection at the time of re-resection for incidental GBC was always performed by 16.7% of respondents ( $n = 34$ ), never performed by 19.7% ( $n = 40$ ) and selectively performed by the remainder if bile spillage had occurred at the time of index cholecystectomy or if port site involvement was suspected on pre-operative imaging.

### Post-operative surveillance, chemotherapy and radiotherapy

Post-operative surveillance was most commonly performed via CT scan (174 respondents, 85.7%, Supplementary Table 1).

Many respondents stopped surveillance 5 years post-operatively (106, 52.2%), while 37 respondents (18.2%) continued lifelong surveillance for their patients.

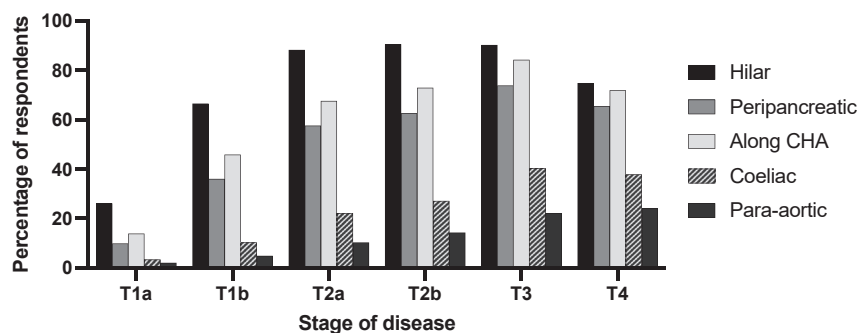
Neoadjuvant chemotherapy was given routinely by only 2 respondents (1%). 26.7% and 43.1% of respondents would consider neoadjuvant chemotherapy for confirmed common hepatic artery or peripancreatic nodes and coeliac, SMA or paraaortic nodes respectively (Supplementary Table 2). Vascular involvement was considered to be the most common indication for neoadjuvant radiotherapy (by 13.3% of respondents).

Over 83% of respondents felt post-operative chemotherapy to be indicated for all N1, N2, or R1 disease and for all T3 stages and above, while 119 respondents (59.8%) considered all tumours at T2 stage and above to be an indication for adjuvant chemotherapy (Supplementary Table 2). Post-operative radiotherapy was felt to be indicated predominantly for R1 or R2 disease independent of T and N stage (84 respondents, 42%). Some 13.5% of respondents used post-operative radiotherapy for all T4 tumours regardless of N stage, and 13% used this for local recurrence only. Post-operative radiotherapy was never routinely used by 102 (51%) respondents.

### Discussion

This is the first global survey of working practices in the management of gallbladder cancer, which has highlighted some interesting differences across many aspects including the diagnostic work up, degree of MDT involvement in decision-making and operative extent. We identified variation in practice between high and low volume units as well as specific areas of divergence from the recommendations of current evidence from the published literature and consensus guidelines.

Not unexpectedly, discussion of GBCs at HPB specific MDTs (or “tumour boards”) happened more frequently in units performing high volumes of liver resections, commensurate with the need for subspecialised MDTs due to greater case volumes.<sup>10</sup> Despite recommendations for routine staging laparoscopy in consensus guidelines, less than one third of respondents overall and less than one fourth of respondents from high volume



**Figure 3** Extent of lymphadenectomy routinely performed. The percentage of respondents selecting the various options is shown on the y-axis, and the T-stages on the x-axis

centres performed this routinely, while MRI and PET CT were in turn underutilised as staging investigations in low volume centres.<sup>1,7-9</sup> Ensuring consistent discussion of GBCs in HPB MDTs may overcome some of these differences in practice, and prove a helpful endeavour towards more uniform and evidence-based staging approaches in the workup of GBC.

The findings of this survey indicate that a more aggressive approach is taken by the wider HPB surgical community towards resection of GBC than suggested by the published consensus guidelines. Involvement of coeliac, superior mesenteric artery and para-aortic nodes (previously considered to be N2 under the 7th AJCC TNM classification) would be considered contraindications to surgery for GBC under these guidelines due to the lack of survival benefit, however approximately half of respondents stated they would proceed with surgery if involvement of these nodes was suspected. In addition, involvement of regional nodes (common hepatic artery or peripancreatic nodes), even if biopsy-confirmed, would not preclude surgery for the majority of respondents, contrary to the recommendation of guidelines for consideration for neoadjuvant chemotherapy in this group of patients due to the poorer prognosis.<sup>1</sup> Around half of respondents would also consider proceeding with resection in the presence of solitary right-sided liver metastases despite the poorer prognosis associated with metastatic disease in this context and the lack of robust evidence to support this. Some of these management decisions may be influenced by unit or country-specific factors including the availability or cost of some diagnostic modalities such as endoscopic ultrasound or neoadjuvant or adjuvant chemotherapy options.

The oncological benefits of minimally invasive approaches to GBC resection have not been widely published to date, although there are recent non-randomised studies suggesting no detriment in outcomes.<sup>11-15</sup> Respondents to this survey adopted a laparoscopic or robotic approach less frequently when liver resection or lymphadenectomy was required, which may be related at least in part to issues of cost, technical complexity (particularly for re-resection in incidental GBC) and concerns around the adequacy of nodal clearance and obtaining R0 resections. Randomised-controlled studies are needed to provide robust confirmation of non-inferiority of outcomes from a minimally invasive approach for GBC, which would facilitate a quicker recovery and commencement of adjuvant treatment.

As demonstrated in other published studies, the extent of resection performed for individual stages of GBC differed by respondents.<sup>16</sup> T1b cancers and above were most frequently managed by radical cholecystectomy (liver resection, either non-anatomical/wedge or segment IVb/V resection) and lymphadenectomy, commensurate with consensus guidelines issued by multiple international societies.<sup>1,7,8</sup> The responses from this survey suggest that wedge resections were favoured for T1b and T2a tumours and more extensive resections were preferred for higher stage tumours. Consensus guidelines currently

recommend a parenchyma-preserving approach in GBC resections, however this continues to be debated in many publications, and in this study less than 1 in 4 respondents considered a non-anatomical liver resection for T3 tumours and above.<sup>1,4,7,9,17</sup>

Lymphadenectomy has been shown to afford a stage-matched survival benefit and avoids understaging and associated undertreatment, and therefore current guidelines recommend lymphadenectomy to be routinely performed for T1b tumours and above. Some guidelines specify the need for retrieval of at least six nodes, thus often requiring lymphadenectomy beyond the hilar nodes alone.<sup>1,7,8,18-21</sup> Accordingly, most respondents reported routine resection of hilar nodes, peripancreatic and common hepatic artery nodes for stages T1b and above in this survey. However, in keeping with recent publications showing inconsistent rates of lymph node retrieval, around one in four respondents did not report routine hilar lymphadenectomy even at higher stages of disease.<sup>18,21-24</sup>

Excision of the CBD was uncommonly performed by most respondents however a small proportion reported performing this routinely, outside of the published guidelines which indicate a lack of survival benefit for routine hepaticojejunostomy unless necessary to achieve an R0 resection.<sup>1,7-9,25-27</sup> Similarly, port site excision was rarely performed routinely by the vast majority of respondents due to reported increased morbidity and a lack of effect on survival,<sup>2,7,28,29</sup> but still performed in all cases by a minority. The reasons for this continued practice despite the clear evidence of increased morbidity are unclear and may represent need for better dissemination of the published guidelines in these areas.

Responses regarding post-operative surveillance were broadly adherent to consensus guidelines, although to date there has not been a recommendation regarding the duration of surveillance.<sup>1,7</sup> Recent clinical trials have demonstrated potential benefit of adjuvant chemotherapy in node positive and higher T stage tumours, and the majority of respondents followed the consensus guidelines in recommending such cases for adjuvant chemotherapy.<sup>1,7-9,30</sup> There was however less consistency with the guidelines regarding recommendation of chemoradiotherapy for margin positive disease.<sup>1,7-9,30</sup>

As with any survey, there are inevitable limitations to this study. Nuances around management decisions are difficult to capture in a survey questionnaire, hence it is impossible to obtain a thorough and comprehensive picture of the management practice around GBC globally from a survey alone. In addition, management practices reported on a survey may differ from actual practice, and the clinician survey format does not allow correlation of variations in management to patient outcomes. The survey was sent out to members of HPB associations who are more likely to work in tertiary or high volume centres, and the practice in smaller centres may therefore not have been completely captured. Furthermore, it would have been of great

interest to compare specific practices between units with high versus low rates of GBC resection, and further analyses of correlations with the HDI index, however many subgroups unfortunately consisted of too small numbers to allow meaningful analyses to be performed.

In conclusion, this study constitutes the largest international survey to date regarding the management of GBC. We have identified heterogeneity of practice in specific areas such as staging investigations, extent of liver resection and lymphadenectomy and CBD or port site resection, where the management undertaken diverges from some of the current guidelines and evidence. These areas would represent useful avenues for further investigation to understand some of the limitations behind the uptake of these recommendations. Our findings could form a springboard for future studies to explore and potentially minimise the heterogeneity in the management of GBC and highlight the need for more widespread collaboration at an international level to identify areas for improvement in GBC outcomes.

#### Collaborating co-authors

OMEGA-S Collaborative Study Group:

Abe T, Achalandabaso M, Adham M, Ahmet A, Al-Sarireh B, Albiol Quer M, Alconchel F, Alsammani M, Alseidi A, Anand A, Anselmo A, Antonakis P, Arabadzchieva E, de Aretxabala X, Aroori S, Ashley S, Ausania F, Banerjee A, Barabino M, Bartlett A, Bartsch F, Belli A, Beristain-Hernandez J, Berrevoet F, Bhatti ABH, Bhojwani R, Bjornsson B, Blaz T, Byrne M, Calvo MP, Castellanos J, Castro MJ, Cavallucci D, Chang D, Christodoulis G, Ciaccio O, Clavien PA, Coker A, Conde-Rodriguez M, D'Amico FE, D'Hondt M, Daams F, Dasari BVM, De Bellis M, de Meijer VE, Dede K, Deiro G, Delgado FJB, Desai G, Di Gioia A, Di Martino M, Dixon M, Dorovinis P, Dumitrascu T, Ebata T, Eilard MS, Erdmann J, Erkan M, Famularo S, Felli E, Fergadi M, Fernandez GB, Fox A, Galodha S, Galun D, Ganandha S, Garcia RJR, Gemenetis G, Giannone F, Gil L, Giorkakis E, Giovinazzo F, Giuffrida M, Giuliani T, Giulianti F, Gkekas I, Goel M, Goh BK, Gomes A, Gruenberger T, Guevara O, Gulla A, Gupta A, Gupta R, Hakeem AR, Hamid HKS, Heinrich S, Helton S, Hernandez-Alejandro R, Heumann A, Higuchi R, Hughes D, Inarejos BC, Ivanecz A, Iwao Y, Iype S, Jaen I, Jie MJ, Jones R, Kacirek K, Kalayarsan R, Kaldarov A, Kaman L, Kanhere H, Kapoor VK, Karanicolos P, Karayiannakis A, Kausar A, Khan ZA, Kim D-S, Klose J, Knowles B, Koh PS, Kolodziejczyk P, Komorowski AL, Koong JK, Kozyrin I, Krishna A, Kron P, Kumar N, van Laarhoven S, Lakhey PJ, Lanari J, Laurenzi A, Leow VM, Limbu Y, Liu Y-B, Lob S, Lolis E, Lopez-Lopez V, Lozano RC, Lundgren L, Machairas N, Magouliotis D, Mahamid A, Malde D, Malek A, Malik H, Malleo G, Marino MV, Mayo SC, Mazzola M, Memeo R, Menon K, Menzulin R, Mohan R, Morgul H, Moris D, Mulita F, Muttillio EM, Nahm C, Nandasena M, Nashidengo PR, Nickkholgh A, Nikov A, Noel C, O'Reilly D, O'Rourke T, Ohtsuka M, Omoshoro-Jones JAO, Pandanaboyana S, Pararas N, Patel R, Patkar S, Peng JS, Perfecto A, Perinel J, Perivoliotis K, Perra T, Phan MT, Piccolo G, Porcu A, Primavesi F, Primrose J, Pueyo-Periz E, Radenkovic D, Rammohan A, Rowcroft A, Sakata J, Saladino E, Schena CA, Scholer A, Schwarz C, Serrano P, Silva M, Soreide K, Sparrelid E, Stattner S, Stuesson C, Sugiura T, Sumo M, Sutcliffe R, Teh C, Teo JY, Tepetes K, Thapa PB, Thepbunchonchai A, Torres JBP, Torres OJM, Torzili G, Tovikkai C, Troncoso A, Tsouffas G, Tuzuher A, Tzimas G, Umar GI, Urbani L, Vanagas T, Varga, Velayutham V, Viganò L, Wakai T, Yang Z, Yip V, Zacharoulis D, Zakharov EA, Zimmitti G.

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#### Declarations of interest

None.

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#### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.hpb.2022.06.014>.