



PRISMA 2009 Checklist

Section / topic	#	Checklist item	Reported on page #
TITLE			
Title	1	For initially unresectable hepatocellular carcinoma: conversion therapy and the suitable timing for subsequent salvage surgery	1
ABSTRACT			
Structured summary	2	<p>Abstract Aim The aim of this narrative review was to review the conversion therapy for initially unresectable hepatocellular carcinoma(HCC) patients and the possible timing for subsequent salvage surgery. Methods A pubmed search was undertaken from 1987 to 2017 to identify articles using the keywords“unresectable hepatocellular carcinoma”, “hepatectomy”, “conversion therapy”, “resection” , “salvage surgery” and “downstaging”. Additional studies were investigated through a manual search of the references from the articles. The main and widely used conversion therapies and the timing for subsequent salvage surgery were discussed in detail. Two members of our group independently performed the literature search and data extraction. Results Liver volume measurement (future liver remnant/total liver volume or residual liver volume/body weight ratio) and function tests (scoring systems and liver stiffness) are often performed in order to justify whether patients are suitable candidates for surgery. Successful conversion therapy is usually defined as downstaging the tumor, increasing future liver remnant(FLR) and providing subsequent salvage surgery, without increasing complications, morbidity or mortality. The requirements for performing salvage surgery after transcatheter arterial chemoembolization(TACE) are the achievement of a partial remission in radiology, the disappearance of the portal vein thrombosis(PVT), the lack of extrahepatic metastasis. Patients with an FLR>20% are good candidates for surgery after portal vein embolization(PVE), while other predictive parameter like growth rate (GR), kinetic growth rate(KGR) are treated as an effective supplementary to the assessment. There is probably not enough evidence to provide a standard operation time after ALLPS or yttrium-90 microsphere RE. The indications of any combinations of conversion therapies and the subsequent salvage surgery time need to be carefully and comprehensively evaluated. Conclusion Conversion therapy is recommended for the treatment of initially unresectable HCC, and the subsequent salvage surgery time should be reappraised and is closely related to its previous therapeutic effect.</p>	2
INTRODUCTION			
Rationale	3	Hepatectomy is currently the first-line curative therapy with prolonging patients’ survival time, but only 10% to 30% of lesions are resectable at the time of diagnosis. Previous studies have confirmed the use of PVE and ALPPS can make initially unresectable HCC resectable. Furthermore, many others treatment could also challenge the resectability such as TACE, RE, but few studies reported about using these methods as conversion therapy. Instead, the majority of research are treatment without surgery.	3
Objectives	4	The aim of this narrative review was to review the conversion therapy for initially unresectable hepatocellular carcinoma(HCC) patients and the possible timing for subsequent salvage surgery, which may provide guideline for clinical practice.	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. (NONE)	--



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Eligibility criteria	6	(1)RCT(2)patients with age above 18 or animal studies(3)treatment used as conversion therapy to increase resectability of HCC(4)threshold for surgery after conversion therapy(4)treatments without conversion therapy or conversion therapy without achieving safe cutoff are excluded. (5) studies using treatment as neoadjuvant therapy is excluded.	--
Information sources	7	A literature search was performed in PubMed (1987-2017) without language restriction.	5
Search	8	using the keywords“unresectable hepatocellular carcinoma”, “hepatectomy”, “conversion therapy”, “resection” , “salvage surgery” and “downstaging”, “portal vein embolization”, “transcatheter arterial chemoembolization ” yttrium-90 microsphere radioembolization” “associating liver partitioning and portal vein occlusion for staged hepatectomy ”. Additional studies were investigated through a manual search of the references from the articles.	5
Study selection	9	Firstly, we removed duplication before excluding studies according to the title and abstract. After that studies were evaluated in more details through reading the full text and selected according to the eligibility criteria. All data were extracted independently by two reviewers (ZZF and LYJ). Discrepancies were discussed with a third reviewer(SWH)	--
Data collection process	10	All data were extracted independently by two reviewers (ZZF and LYJ). We extracted data from the databases of PubMed (1987-2017). Then duplicates were removed before screening records and excluding records according to titles and abstracts. Finally, full-text articles were assessed for eligibility. Discrepancies were discussed with a third reviewer (SWH).	--
Data items	11	Title, author, publication year, number of patients, disease type, schedule of conversion therapy, therapy duration, observation period, timing for surgery, types and rate of postoperative complication, overall survival disease-free survival, FLR, Tumor necrosis in radiology, liver function parameters.	--
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	--
Summary measures	13	types and rate of postoperative complication, overall survival disease-free survival, FLR, Tumor necrosis in radiology, liver function parameters.conversion rate.	5
Synthesis of results	14	Liver volume measurement (future liver remnant/total liver volume or residual liver volume/body weight ratio) and function tests (scoring systems and liver stiffness) are often performed in order to justify whether patients are suitable candidates for surgery. Successful conversion therapy is usually defined as downstaging the tumor, increasing future liver remnant(FLR) and providing subsequent salvage surgery, without increasing complications, morbidity or mortality. The requirements for performing salvage surgery after transcatheter arterial chemoembolization(TACE) are the achievement of a partial remission in radiology, the disappearance of the portal vein thrombosis(PVT), the lack of extrahepatic metastasis. Patients with an FLR>20% are good candidates for surgery after portal vein embolization(PVE), while other predictive parameter like growth rate (GR), kinetic growth rate(KGR) are treated as an effective supplementary to the assessment. There is probably not enough evidence to provide a standard operation time after ALLPS or yttrium-90 microsphere RE. The indications of any combinations of conversion therapies and the subsequent salvage surgery time need to be carefully and comprehensively evaluated.	2

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Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	--
Additional analyses	16	We insert some tables to illustrate the characteristic of conversion therapies.	42-45
RESULTS			
Study selection	17	<pre> graph TD A["using key words search: 'unresectable hepatocellular carcinoma', 'hepatectomy', 'conversion therapy', 'resection', 'salvage surgery' and 'downstaging', 'portal vein embolization', 'transcatheter arterial chemoembolization', 'yttrium-90 microsphere radioembolization' " associating liver partitioning and portal vein occlusion for staged hepatectomy" in pubmed from 1968 to 2018. Number of articles identified by manual search=31431. The last search is on 2018-05-14. The total search frequency is"] --> B["Review the abstract"] A --> C["duplicates removed"] B --> D["Full text evaluated based on eligible eligibility criteria"] B --> E["case report case series video unrelated to conversion therapy comment editorial essays"] D --> F["studies included(n=110)"] </pre>	--
Study characteristics	18	Of 31431 studies, we excluded duplicates, case reports ,case series , video, content unrelated to conversion therapy, comment, editorial assay. Finally, a total of 110 assay fulfil the inclusion criterion.	--
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	--
Results of individual studies	20	Of 110 studies included, 2 studies refer to safe timing after TACE, 9 refer to safe timing after PVE, 1 mention safe cutoff before stage2 in ALPPS, 0 refer to safe threshold after Y-90 RE, 3 refer to TACE + PVE. Other studies indirectly refer to safe cutoff as well as possible improved survival time.	--
Synthesis of results	21	Liver volume measurement (future liver remnant/total liver volume or residual liver volume/body weight ratio) and function tests (scoring systems and liver stiffness) are often performed in order to justify whether patients are suitable	5-20



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		candidates for surgery. Successful conversion therapy is usually defined as downstaging the tumor, increasing future liver remnant (FLR) and providing subsequent salvage surgery, without increasing complications, morbidity or mortality. The requirements for performing salvage surgery after transcatheter arterial chemoembolization (TACE) are the achievement of a partial remission in radiology, the disappearance of the portal vein thrombosis (PVT), the lack of extrahepatic metastasis. Patients with an FLR > 20% are good candidates for surgery after portal vein embolization (PVE), while other predictive parameters like growth rate (GR), kinetic growth rate (KGR) are treated as an effective supplementary to the assessment. There is probably not enough evidence to provide a standard operation time after ALLPS or yttrium-90 microsphere RE. The indications of any combinations of conversion therapies and the subsequent salvage surgery time need to be carefully and comprehensively evaluated.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	--
Additional analysis	23	We insert some tables to illustrate the characteristic of conversion therapies.	42-45
DISCUSSION			
Summary of evidence	24	Conversion therapy is recommended for the treatment of initially unresectable HCC, and the subsequent salvage surgery time should be reappraised and is closely related to its previous therapeutic effect.	21
Limitations	25	Firstly, this is a narrative review which didn't systematically analyse the topic because the concept of conversion therapy is rarely mentioned in the studies, and many information are extracted by manual job rather than being mentioned directly by the author. This specificity limited our previous aim to make it a systematic review even a meta-analysis. Secondly, our review didn't provide information about risk of bias, for that the available essays are insufficient to form any meta-analyses.	21
Conclusions	26	Conversion therapy is recommended for the treatment of initially unresectable HCC, and the subsequent salvage surgery time should be reappraised and is closely related to its previous therapeutic effect.	21
FUNDING			
Funding	27	No funding	2

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