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Original Research

Changing trends in hepatocellular carcinoma management: Results from a nationwide database in the last decade

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Abstract ***Objective:*** The therapeutic strategies for hepatocellular carcinoma (HCC) have greatly expanded in recent years. However, the actual usage of each of these treatments in clinical routine remains unknown. Here, we analysed the distribution and changes of the main surgical and radiological therapeutic procedures nationwide during the last decade.
Methods: Retrospectively, analysis of the data on all >18-year-old patients with a diagnosis of HCC identified in the French Program for the Medicalization of Information Systems database that contains all discharge summaries from all French hospitals. The number and percentage of the therapeutic procedures performed from January 2010 to December 2019 were extracted.
Results: A total of 68,416 therapeutic procedures were performed in 34,000 HCC patients. Whereas HCC incidence remained stable, the annual number of procedures frankly increased over the decade (from 4267 to 8042). Trans-arterial chemoembolization was the most frequently performed technical procedure, with a double-digit annual growth from 2010 (n = 1932) to 2015 (n = 4085), before stabilization from 2016. Selective internal radiation

Abbreviations: HCC, hepatocellular carcinoma; TACE/TAE, trans-arterial chemo/embolization or embolization; SIRT, selective Yttrium-90 internal radiation; OLT, orthotopic liver transplantation.

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therapy displayed the highest increase in the decade (+475%). Among curative treatments, the annual number of percutaneous tumour ablations more than doubled in 10 years, till representing 64% of curative treatments in cirrhotic patients in 2019. Surgical tumour resections showed a 1.5-fold increase in 10 years, due to the great increase in minimally invasive approaches, whereas the proportion of open resection progressively decreased.
Conclusion: Minimally invasive procedures have gained major importance in HCC management during the last decade. Percutaneous thermal ablation has emerged as the first curative treatment performed for patients with HCC.

1. Introduction

The management of patients with HCC is complex because of the underlying cirrhotic disease, and the patient prognosis is influenced equally by the tumour stage and the severity of the underlying liver disease. The choice of treatment requires optimising the balance between maximum antitumour efficacy and limited liver toxicity [1–3]. In this context, several minimally invasive radiological procedures, local or locoregional, have been developed in the last two decades. Different percutaneous tumour ablation techniques have become widely available with the development of microwave thermal ablation, multibipolar radiofrequency and irreversible electroporation. Concerning intra-arterial therapies, trans-arterial chemoembolization (TACE) has been the reference treatment for BCLC B stage HCC for long time, and many efforts have been done to improve its tolerance [4,5]. Moreover, Yttrium-90 selective internal radiation therapy (SIRT) is rapidly expanding, although its precise place in HCC management remains to be defined [6]. Surgical techniques have also benefitted from many improvements, particularly the development of minimally invasive laparoscopic and/or robotic tumour resection [7,8].

The constant progress and refinement of HCC multidisciplinary management can be disturbing for non-specialised physicians and patients. Therefore, it is important to analyse the place and role of all these procedures in real life in large non-selected populations. In this study, we extracted data from an exhaustive national database that contains the discharge summaries from all French hospitals to analyse the changes over the last 10 years of the various technical procedures available for HCC management. Knowing the use of the different therapies in large populations might help to understand their place in real-life HCC management, to assess their acceptance by the medical community, and to make projections for the coming years. Specifically, France provides an interesting epidemiological model for HCC, as it is representative of many western countries. The incidence of HCC is certainly lower than in sub-Saharan or Asian countries but is high enough to constitute a real public health issue [9]. As in many western countries, alcohol consumption, hepatitis C and metabolic-associated fatty liver disease are the main causes of chronic liver disease [10,11]. Because of an insufficient or inadequate organised screening, the majority of HCCs remain diagnosed at intermediate or advanced stages [12]. However, the distribution of university hospitals throughout the country and free access to care for all make it possible to propose high-resource level treatments for most patients.

The objective of our study was to analyse the distribution and changes of the main surgical and radiological therapeutic procedures using an exhaustive French nationwide database during the last decade (2010–2019).

2. Methods

2.1. Study design and data source

This retrospective nationwide cohort study adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines. It was approved by the institutional review board of Montpellier University Hospital (IRB CHU de Montpellier), who waived patients informed consent because of the retrospective analysis of an anonymised database, and was registered at clinicaltrials.gov (NCT 04163627). Data were extracted from the French Program for the Medicalization of Information Systems database that contains all discharge summaries from all hospitals nationwide. Discharge summaries include information on the patient demographics, principal and associated diagnosis codes according to the tenth revision of the International Classification of Diseases (ICD-10), procedure codes, mode of hospitalization, duration of hospital stay and hospital identification code. Each patient has an anonymous alphanumerical identifier that allows tracing all hospital admissions in the country. This database has been regularly used for epidemiological studies, including on HCC [12,13].

Table 1
Demographic and clinical data of the 69,578 patients admitted in hospitals for HCC in France, and of those admitted for a therapeutic procedure (n = 34,000, i.e. study population) from 1st January 2010 to 31st December 2019.

	All patients N = 69,578	Study population N = 34,000
Men	56,933 (81.8)	28,504 (83.8%)
Age at 1st admission, years		
Mean (SD)	68.1 (±11.1)	66.5 (±10.2)
Median (Q_{25};Q_{75})	68.0 (61.0;76.0)	67.0 (60.0; 74.0)
Range	[18.0;103.0]	[18.0; 97.0]
New patients per year		
- 2010	8218 (11.8)	3266 (9.6)
- 2011	6692 (9.6)	2986 (8.8)
- 2012	6592 (9.5)	3169 (9.3)
- 2013	6477 (9.3)	3218 (9.5)
- 2014	6620 (9.5)	3342 (9.8)
- 2015	6947 (10.0)	3606 (10.6)
- 2016	6844 (9.8)	3483 (10.2)
- 2017	7090 (10.2)	3637 (10.7)
- 2018	7124 (10.2)	3721 (10.9)
- 2019	6974 (10.0)	3572 (10.5)
HCC incidence (per 100,000)*		
- 2010	12.7	
- 2011	10.3	
- 2012	10.1	
- 2013	9.9	
- 2014	10.0	
- 2015	10.5	
- 2016	10.3	
- 2017	10.6	
- 2018	10.7	
- 2019	10.4	
Cirrhosis	45,347 (65.2)	25,272 (74.3)
Diabetes	23,825 (34.2)	12,836 (37.8)
Hypertension	30,525 (43.9)	16,876 (49.6)
Number of admissions per patient		
Mean (SD)	2.13 (±1.8)	2.9 (±2.1)
Median (Q_{25}-Q_{75})	1.0 (1.0; 3.0)	2.0 (1.0; 4.0)
Range	[1.0; 55.0]	[1.0; 30.0]
Patients with at least one of the following procedure:		
- Percutaneous thermal ablation	10,835 (15.6)	10,835 (31.9)
- Operative tumour ablation	977 (1.4)	977 (2.9)
- Mini-invasive surgical resection	2990 (4.3)	2990 (8.8)
- Open surgical resection	8673 (12.5)	8673 (25.5)
- Orthotopic liver transplantation	2323 (3.3)	2323 (6.8)
- TACE/TAE	17,639 (25.4)	17,639 (51.9)
- SIRT	1453 (20.9)	1453 (4.3)
Number of procedures per patient		
Mean (SD)		2.0 (±1.4)
Median (Q_{25}-Q_{75})		1.0 (1.0; 3.0)
Range		[1.0; 17.0]
Number of procedures per patient		
- 1		17,280 (50.82)
- 2		7939 (23.35)
- 3		4288 (12.61)
- 4		2280 (6.71)
- 5		1098 (3.23)
- 6		558 (1.64)
- ≥7		557 (1.64)

Unless otherwise indicated, results are expressed as numbers (percentage).
HCC incidence reports the ration between *de novo* HCC patients per year based on PMSI data and the annual French population estimated by INSEE (French National Institute of Statistics and Economical Studies, =https://www.insee.fr/fr/statistiques/4277615?sommaire=4318291#consulter-sommaire).

2.2. Data extracted

All hospital summaries of >18-year-old patients with a diagnosis of HCC (i.e. ICD-10 code C22.0: liver cell carcinoma − HCC or hepatoma) from 1st January 2010 to 31st December 2019 were extracted from the database. Admissions with the C22.9 code (malignant neoplasm of liver, unspecified) were also screened and included in the analysis, if they had the C22.0 code at follow-up. Then, only patients with one or more of the following procedure codes were selected: percutaneous tumour destruction (HLNM001/HLNK001/HLNN900), operative tumour ablation (surgical approach) (HLNC003/HLNA007), open liver resection (HLFA003/HLFA004/HLFA005/HLFA006/HLFA007/HLFA009/HLFA010/HLFA011/HLFA017/HLFA018/HLFA019/HLFA020), minimally invasive (laparoscopic/robotic) liver resection (HLFC002/HLFC003/HLFC004/HLFC027/HLFC032/HLFC037/HLFC801), orthotopic liver transplantation (OLT) (HLEA002/HLEA001), trans-arterial chemoembolization or embolization (TACE/TAE) (EDLF014/EDLF015/EDLF016/EDLF017) and Yttrium 90 SIRT (EDLL001/EDLL002). For this sample, the following data were collected: age, sex, cirrhosis, associated diseases (diabetes, hypertension, obesity) and number and percentage per year of the procedures listed above. The number of hospitals per year in which one of the studied procedures was performed (and the number of these hospitals with a caseload >10 and >25 patients/year) were also collected.

2.3. Statistical analysis

All analyses were carried out by the Department of Research and Medical Information at Montpellier University Hospital using the SAS statistical software (SAS Enterprise Guide, version 7.13; SAS Institute; Cary, North Carolina, USA). Quantitative data were expressed as means ± standard deviation (SD), and categorical data as numbers (percentages). For each procedure category, the following data were calculated: total number and percentage of procedures per year and total number and percentage of patients who underwent that procedure per year.

3. Results

3.1. Study population

In total, 148,535 hospital admissions for 69,578 patients with the main diagnosis of HCC were retrieved from the

HCC, hepatocellular carcinoma; N, number; SD, standard deviation; Q_{25}, 25th quartile; Q_{75}, 75th quartile; TACE/TAE, Trans-arterial chemo/embolization; SIRT, selective internal radiation therapy.

database for the study period. Among all these hospitalizations, 68,416 concerned surgical or radiological therapeutic procedures in 34,000 patients (i.e. the study population). The demographic and clinical characteristics of the study population are summarised in Table 1. The annual incidence of HCC remained globally stable over the years (between 9.9 and 10.7/100,000 except for 2010), as well as the proportion of newly treated HCC patients (from 9.1 to 10.9% of the study population). Conversely, the yearly number of procedures (from 4267 in 2010–8042 in 2019; +88.5%) and the yearly number of patients who had at least one procedure (from 3266 in 2010–5750 in 2019; +76.1%), increased every year. Half of the patients had only one procedure, but the mean number of procedures per patient was 2 (±1.4). The changes in the number of procedures and percentage of patients who underwent such procedures in the last 10 years are shown in Figs. 1 and 2, and detailed in eTable 1–4 in Supplement 1, for the whole population and for the subgroup of patients with cirrhosis.

3.2. Palliative procedures

Over the past decade, TACE/TAE was the most frequently performed technical procedure for the treatment of patients with HCC. The total number of TACE/TAE procedures increased markedly from 2010 (n = 1932) to 2015 (n = 4085) with a double-digit annual growth and more than twofold increase, before becoming stable from 2016, and even declining in 2019 (n = 3522) (Fig. 1). During the study period, TACE/TAE was performed in 51.9% of patients admitted for a technical procedure (17,639/34,000), with a nadir at 44% in 2011 and 2019, and a zenith at 53% in 2014 in the whole population and a nadir at 48% in 2011 and 2019 and a zenith at 56% in 2013 and 2014 in the group with cirrhosis.

SIRT increased from 88 procedures in 2010 to 506 in 2019 and was performed in 2% and 5.7% of patients admitted for a technical procedure in 2010 and in 2019, respectively. Among all the studied procedures, SIRT displayed the highest growth rate in the 10 years (+475%, Table 2).

3.3. Curative procedures

The yearly number of percutaneous tumour ablations increased sharply and more than doubled in 10 years, from 1014 in 2010–2102 in 2019 (growth rate of +107% for the 10 years) (Fig. 1, Table 2). Operative tumour ablations also increased (growth rate of 82% for the 10 years), but their absolute numbers remained low (n = 120 procedures in 2019). The number of surgical resection procedures also increased from 1001 in 2010 to 1468 in 2019 (approximately 1.5-fold increase). However, because of the marked increase of TACE/TAE and thermal ablation procedures, the proportion of surgical resection procedures slowly but persistently decreased from 23.5% of all procedures in 2010 to 18.3% in 2019. Open liver resection remained almost stable during the study period (growth rate of 7% for the decade), whereas minimally invasive liver resection strongly increased from 132 procedures in 2010 to 540 in 2019 (growth rate of 309% for the decade). OLT increased regularly (growth rate of +95% for the decade) and reached 324 procedures in 2019.

3.4. Distribution of curative treatments

The changes in distribution of curative treatments from 2010 to 2019 are described in Fig. 3. Surgical resection and thermal ablation represented 45% and 48% of all curative treatments in 2010 and 46% in 2011. However, thermal ablation procedures then became the first curative treatment for patients with HCC (55% of curative treatments versus 37% of surgical resection in 2019). The difference was even more pronounced in the group with cirrhosis where thermal ablation increased from 56% of all curative treatments in 2010 to 64% in 2019, and surgical resection decreased from 35% in 2010 to 25% in 2019.

The percentage of patients who underwent percutaneous thermal ablation increased from 27.8% in 2010 to 32.8% of patients (+5%) in 2019. Similarly, the percentage of patients treated by minimally invasive surgical resection increased from 3.9% in 2010 to 8.8% in 2019 (+5%). Conversely, the percentage of patients with open surgical resection decreased from 24.7% to 14.8% (−10%) (Fig. 2). The increase of percutaneous thermal ablation and minimally invasive surgical resection was observed also in the group with cirrhosis (from 30.5% to 3.5% of patients in 2010 to 35.8% and 6.7% in 2019, i.e. +5.3% and +3.2%, respectively). Conversely, the percentage of patients admitted for open liver resection decreased from 17.9% to 8.6% (−9.3%).

3.5. Changes in the territorial offer of technical procedures

The number of hospitals per year in which one of the studied procedures was performed is shown in eTable 5 in Supplement 1. The number of centres that performed open surgical resections (approximately 150) remained almost stable in the last 10 years. On the other hand, the number of centres that propose percutaneous thermal ablation and minimally invasive liver resection increased from 74 to 52 in 2010 to 104 and 94 in 2019, respectively. In the same way, the number of centres with a caseload >10 and >25 patients per year that perform percutaneous thermal ablation and minimally invasive liver resection frankly increased from 2010 to 2019. Finally, the number of centres performing both percutaneous thermal ablation and minimally invasive surgical resection increased from 25 in 2010 to 59 in 2019.

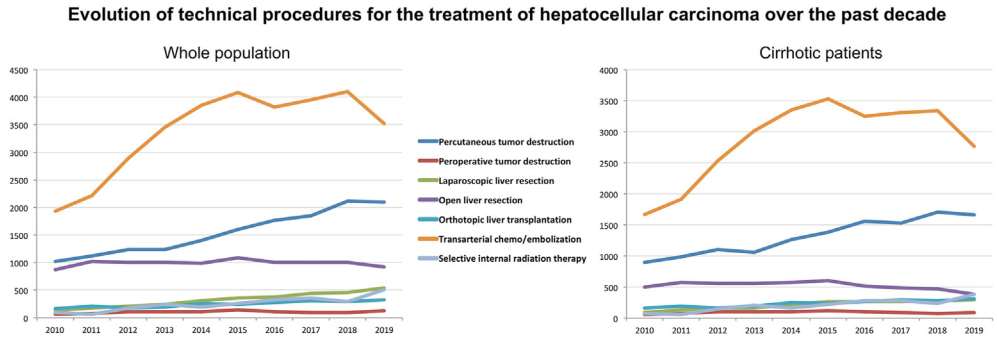

Fig. 1. Changes during the last 10 years in the number of therapeutic procedures used for the management of patients with hepatocellular carcinoma in French hospitals in the whole sample and in patients with cirrhosis. These data show the rise of minimally invasive therapies, such as trans-arterial locoregional procedures and thermal ablation.

4. Discussion

This study, based on a comprehensive national cohort in France brings new insights into the management of patients with HCC. The results confirm the huge development of minimally invasive techniques in the last 10 years. One of the most striking results is the progressively increasing place of percutaneous tumour destruction techniques that have become the first curative procedure for HCC in France since 2014 (55% of all curative treatments in 2019). This is even more evident in the subgroup with cirrhosis, where patients frequently present contraindication to surgery due to portal hypertension or coagulopathy and where thermal ablation represented 64% of all curative treatments in 2019. These data suggest the good acceptability of tumour ablation procedures by patients and hepatologists/oncologists, due to the combination of good oncological efficacy and low morbidity [14]. This sustained and steady growth may also result from the technical progress to improve the targeting of occult or poorly located tumours [15], the treatment of larger HCC using multiple needles [16] and the democratization of these methods that are now regularly used in combination with surgical resection, or as a final treatment in patients who have responded well to other treatments.

If percutaneous thermal ablation displayed a regular growth during the last 10 years, TACE/TAE procedures strongly increased from 2010 to 2015, before becoming stable during the second half of the study period, and possibly starting to decline in 2019. Their exceptional growth from 2010 to 2015 may have been linked to the development of drug-eluting beads [17]. Conversely, the decline observed in 2019, to be confirmed in the next few years, may coincide with advances in systemic treatments, particularly immunotherapy [18] and the caution taken to limit the number of sessions not to impair liver function, which could compromise subsequent systemic treatments [19]. Although SIRT is not included in the decision-making algorithms for HCC treatment, its sharp increase in recent years suggests that physicians have a strong clinical interest for this technique. If many centres have been using this treatment in the framework of randomised clinical trials [20,21] in the first half of the past decade, its use still grew in the second half although those trials turned out to be negative. In a recent phase 2 trial, SIRT performed using a personalised dosimetry approach has shown a great improvement of the objective response rate versus a standard dosimetry approach [22]. This study paves the way for a better understanding of the possibilities of this treatment and will certainly accentuate the renewed interest in the SIRT in the upcoming years.

Concerning surgical resection, considerable efforts have been made to reduce morbidity/mortality and improve the intervention acceptability. Therefore, the continuous decrease in the percentage of open resections for HCC in the past decade has been offset by the growth in the number of laparoscopic resections, due to the improvement of this surgical technique and the expansion of surgical devices (e.g. intraoperative ultrasound, cavitron ultrasonic dissector for liver parenchymal dissection, mechanical staplers) [23–25]. Laparoscopic and robotic resections have some short-term advantages, such as reduced blood loss, lower postsurgical morbidity and shorter hospital stay [7,26,27]. Robotic systems also facilitate resection of tumour located in posterior and superior segments [28].

Epidemiological studies of HCC are common, which contrasts with the paucity of studies analysing trends and distribution of treatment for this cancer. A recent study based on a Dutch nationwide cancer registry database [29] observed an increase in proportion of patients receiving a treatment from 49% in 2009–2010 to 57% in 2015–2016, which was also observed in our results where more treatments were performed over the years. As the HCC incidence remained overall stable over the years in France, and in the absence of significant changes in screening policies, it is likely that the increase in therapeutic procedures performed was linked to the better accessibility or dissemination of mini-

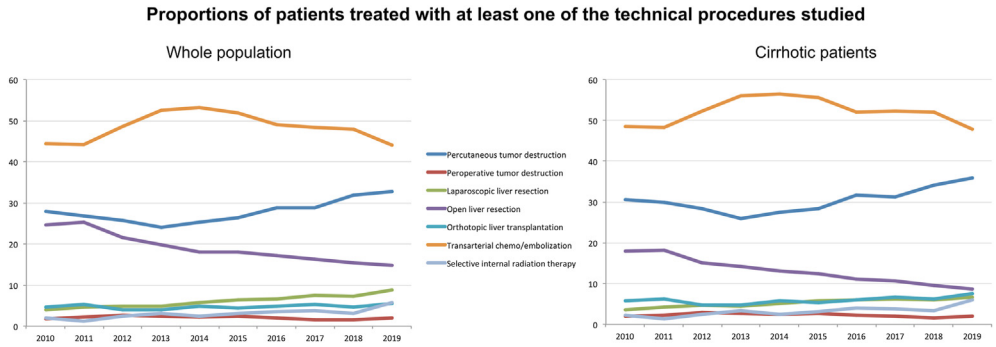

Fig. 2. Changes during the last 10 years in the number of patients with hepatocellular carcinoma treated with at least one of the studied procedures in French hospitals in the whole sample and in patients with cirrhosis. About 50% of patients underwent trans-arterial locoregional treatment.

Table 2
Growth rate (%) in procedure usage in France over the last decade.

	Procedure in 2010 (n)	Procedure in 2019 (n)	Decadal growth rate of procedures (%)	Patients in 2010 (n)	Patients in 2019 (n)	Decadal growth rate of patients (%)
Percutaneous tumour ablation	1014	2102	107	909	1887	108
Operative tumour ablation	66	120	82	62	112	81
Minimally invasive liver resection	132	540	309	127	506	298
Open liver resection	869	928	7	808	851	5
Orthotopic liver transplantation	166	324	95	154	318	106
Trans-arterial chemoembolization	1932	3522	82	1453	2533	74
Selective internal radiation therapy	88	506	475	66	326	394
Total	4267	8042	88	3579	6533	83

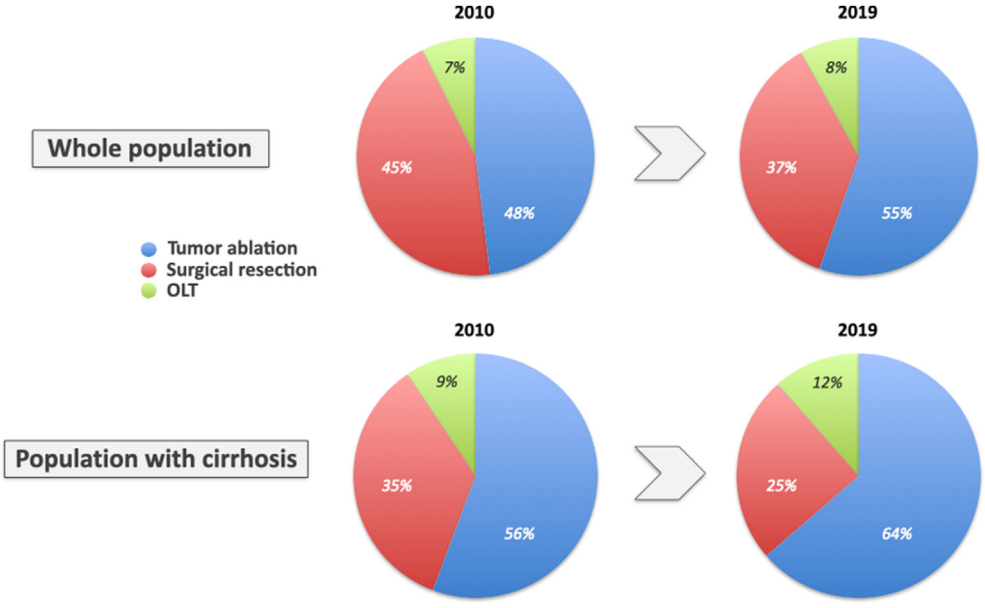

Fig. 3. Changes in the usage frequency of curative treatments for hepatocellular carcinoma from 2010 to 2019.

invasive approaches, which should have made it possible to increase the therapeutic possibilities in patients with hepatic dysfunctions or in borderline general condition. In the BRIDGE study [30], mini-invasive treatments such as TACE or ablation also represented a large proportion of treatment performed either in first or second position but the authors did not look for any temporal trends.

The results of our study clearly highlight the strong tendency to offer more therapeutic solutions to cancer patients, and to favour minimally-invasive approaches. Clinicians should be made aware of the importance of referring their patients to health centres where minimally invasive approaches are widely represented. Efforts should probably also be made to widely spread these techniques, currently limited to large hospitals and cancer centres. Yet, many of these mini-invasive treatments are currently being tested in association with immunotherapies. If positive, combination of immunotherapy and mini-invasive treatments could be a major advance in the preservation of the liver function allowing optimising the tolerance while maintaining a good efficacy.

Our study has some limitations. Indeed, the analysis was based on data from the French Program for the Medicalization of Information Systems database. These data are entered and coded by practitioners and/or administrative staff based on the discharge summary and the procedure description. As hospital invoicing is based on this computerised declaration, many efforts have been made to improve and optimise the coding of procedures and patient data when this system was generalised in the mid-2000s. However, some errors or rather omissions remain possible, especially concerning the associated diseases and comorbidities. This could explain the underrepresentation of the diagnosis of cirrhosis in our study population. Moreover, this database only includes procedures performed in hospitalised patients. As procedures performed in outpatients, such as external radiotherapy, are not included, they were not analysed in our study. Finally, to present results in a clear manner, it was decided to perform the analysis according to a per-procedure and per-patient design, and combined treatments carried out during the same hospital stay were not considered.

5. Conclusion

This study shows unequivocally the major role of minimally invasive image-guided therapies in the management of patients with HCC in France. Intra-arterial locoregional therapies were the most commonly performed procedures, involving more than half of all included patients, and percutaneous tumour ablation techniques have emerged as the first-line curative treatment for HCC. The major growth of SIRT and minimally invasive surgical resection also provides insights into how the therapeutic arsenal for HCC will develop in the next years.

Authors contributions

CC: Conceptualization, Formal analysis, Investigation, Methodology, Supervision, Validation, Writing - original draft, Writing - review & editing. EN: Data curation, Writing - review and editing, Formal analysis. MM: Data curation, Writing - review and editing. FP: Supervision, Writing -review and editing. NM: Conceptualization, Formal analysis, Resources, Software, Validation, BG: Conceptualization, Methodology, Validation.

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Trial registration

ClinicalTrials.gov, Identifier: NCT 04163627.

Conflict of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2021.01.009.

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