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ORIGINAL ARTICLE

Selective internal radiotherapy in Germany: a review of indications and hospital mortality from 2012 to 2019

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ABSTRACT

Background and Aim: Selective internal radiotherapy (SIRT) is a minimal invasive tumor therapy for hepatocellular carcinoma (HCC), biliary tract cancer (BTC), and liver metastasis of extrahepatic tumors. Comprehensive data on past and current trends of SIRT as well as outcome parameters such as in-hospital mortality and adverse events in Germany are missing.
Methods: We evaluated current clinical developments and outcomes of SIRT in Germany based on standardized hospital discharge data, provided by the German Federal Statistical Office from 2012 to 2019.
Results: A total of 11,014 SIRT procedures were included in the analysis. The most common indication was hepatic metastases (54.3%; HCC: 39.7%; BTC: 6%) with a trend in favor of HCC and BTC over time. Most SIRTs were performed with yttrium-90 (99.6%) but the proportion of holmium-166 SIRTs increased in recent years. There were significant differences in the mean length of hospital stay between ^{90}Y (3.67 ± 2 days) and ^{166}Ho (2.9 ± 1.3 days) based SIRTs. Overall in-hospital mortality was 0.14%. The mean number of SIRTs/hospital was 22.9 (SD ± 30.4). The 20 highest case volume centers performed 25.6% of all SIRTs.
Conclusion: Our study gives a detailed insight into indications, patient-related factors, and the incidence of adverse events as well as the overall in-hospital mortality in a large SIRT collective in Germany. SIRT is a safe procedure with low overall in-hospital mortality and a well-definable spectrum of adverse events. We report differences in the regional distribution of performed SIRTs and changes in the indications and used radioisotopes over the years.
Relevance for Patients: SIRT is a safe procedure with very low overall mortality and a well-definable spectrum of adverse events, particularly gastrointestinal. Complications are usually treatable or self-limiting. Acute liver failure is a potentially fatal but exceptionally rare complication. ^{166}Ho has promising beneficial bio-physical characteristics and ^{166}Ho-based SIRT should be further evaluated against ^{90}Y-based SIRT as the current standard of care.

1. Introduction

Selective internal radiotherapy (SIRT) is a therapeutic procedure allowing targeted delivery of short-range high-dose beta radiation to liver tumors for the purpose of brachytherapy. In the early days of SIRT, which was described first in the 60s of the 20th century [1], the procedure was done by laparotomy followed by direct injection of small-sized microspheres loaded with the radioisotope into the hepatic artery, while today, it is done minimal-invasive via catheter through the femoral artery. The most commonly used β-radioisotopes

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for SIRT are yttrium-90 (^{90}Y) and holmium-166 (^{166}Ho), while other promising radioisotopes like Rhenium-188 (^{188}Re) have not gained wide acceptance in Germany. ^{90}Y is available in two different microsphere types (resin microspheres (Sir-Spheres®, Sirtex Medical Ltd., Sydney, Australia) and glass microspheres (Therasphere®, Boston Scientific, Boston, MA, USA) which differ in diameter (32.5 µm vs. 25 µm) and radioactivity (becquerel, Bq) per microsphere (50 Bq vs. 2500 Bq) [2,3]. Despite these different physical properties, different studies showed no difference in terms of overall survival (OS) and safety between the yttrium-based products [4-6]. On the other hand, Holmium is a recently developed agent (approval in Germany in 2015), available as ^{166}Ho-poly-L-lactic acid (PLLA) microspheres (QuiremSpheres®, Quirem Medical B.V., Deventer, The Netherlands) with a diameter of 32µm and an activity of 450 Bq per microsphere [3]. ^{166}Ho has a slightly shorter half-life than ^{90}Y (1.1 vs. 2.7 days as ^{90}Y), and favorable imaging potential due to its paramagnetic properties and additional γ-radiation [7]. Randomized and controlled trials (RCT) comparing yttrium and holmium in terms of tumor effectivity and safety are missing.

SIRT is performed in a lobar, sectorial, or segmental way according to tumor size and location [2]. There are some factors leading to a predominantly effect on tumor tissue compared to liver parenchyma: Tumor tissue supply out of the hepatic artery, the comparatively higher vascular density in most tumors, and the short range of radiation into the tissue (brachytherapy) increases the effect within the tumor tissue while sparing the surrounding liver parenchyma [2,5]. Despite local therapeutic effects, the biological effect of SIRT on healthy liver tissue and its impact on distant toxicity through incorrect embolization or shunting is an important factor [3]. During pre-treatment planning for ^{90}Y-based SIRTs, technetium-99m macro aggregated albumin (MAA) is injected into the hepatic arteries, and the lung shunt (LS) is estimated based on the fraction of MAA which becomes deposited in the pulmonary vasculature to avoid adverse effects (MAA-Scan) [8].

With regard to indications for SIRT, hepatocellular carcinoma (HCC) and biliary tract cancer (BTC) represent the two most common primary hepatic malignancies. Furthermore, SIRT is used in liver metastasis of many different extrahepatic tumor entities such as colorectal cancer (CRC), neuroendocrine tumors (NET), melanoma, and others [9,10]. Compared to alternative treatments such as systemic therapies and transarterial chemoembolization (TACE), SIRT has the advantage of being usually a one-off treatment in most cases [11]. Furthermore, it can be performed when portal vein thrombosis is present; a condition that often excludes patients from TACE, due to the minimal embolic effect of the microspheres [12].

Current European guidelines (European Association for the Study of the Liver [EASL]; European Society for Medical Oncology [ESMO]) for the management of HCC recommend SIRT in very-early and early-stage HCC patients (Barcelona Clinic Liver Cancer (BCLC) 0-A, ≤8cm nodules) as an equally effective alternative to TACE if ablation and resection are not feasible as well as in patients with HCC in stage B after TACE failure or refractoriness, and in BCLC C where no other systemic therapy is feasible (respectively in case of liver confined tumor and good liver function). Furthermore, SIRT can be used with the aim of downstaging the tumor for resection or liver transplantation [13,14].

In liver-limited advanced cholangiocarcinoma, SIRT can be used (as well as other trans-arterial procedures, e.g., TACE) if systemic therapies are not feasible or as an adjunct to systemic therapies and in locally limited intrahepatic cholangiocarcinoma in second-line therapy for selected patients according to current ESMO guidelines [15-18]. Furthermore, SIRT is well-established in clinical practice for treating liver metastasis of different primarily extrahepatic tumors [19-22].

Population-based data about the indication, prevalence, and outcome of SIRT are missing. The heterogeneous indications, different available application forms, and the multiple professionals and sites involved (oncologists, radiologists, physicists, and nuclear medicine specialists) make it increasingly difficult to obtain an overall picture. This study aimed to give a detailed insight into the frequency, outcome, and safety of SIRT over a long observational period in Germany.

2. Materials and Methods

2.1. Study design

The present study represents a retrospective analysis of epidemiological trends as well as in-hospital mortality and adverse events of SIRT in Germany. Analyses are based on standardized hospital discharge data provided by the Federal Statistical Office of Germany (Wiesbaden, Germany) from 2012 to 2019. A contract for remote data analysis was signed between the Federal Statistical Office and the University Hospital Duesseldorf in 2020. Due to the complete anonymization of patient information, no additional ethics approval was necessary.

2.2. Patient eligibility criteria and variables

Identification of the overall study population was performed through the specific treatment approach (SIRT) for each patient using the following OPS-codes: 8-530a5 (^{90}Y), 8-530a6 (^{188}Re), 8-530a8 (^{166}Ho). The main diagnosis of the respective hospital stay using the ICD-10 codes C22.0 (HCC), C22.1 (CCC), and C78.7 (Filiae). Patients with organ complications were identified by the following secondary diagnosis: Acute liver failure (K72.0), acute renal failure (N17), acute pancreatitis (K85.0, K85.1, K85.3, K85.8, and K85.9), acute cholecystitis (K81.0), liver abscess (K75.0), lung abscess (J85.1, J85.2, and J85.3), radiation-induced acute lung injury (J70.0 and J70.4), interstitial pneumonia (J84.8-J84.9), pulmonary embolism (I26.0 and I26.9), acute gastritis (K29.0, K29.1, K29.6, and K29.7), ulcus ventriculi (K25.0), duodenitis (K29.8), ulcus duodeni (K26.0), sepsis (A32.7, A39.2, A39.3, A.40.0, A40.1, A40.2, A40.3, A40.8, A40.9, A40.1, A41.1, A41.2, A41.3, A41.4, A41.51, A41.52, A41.58, A41.8, A41.9, A42.7, A26.7, A0.21, A20.7, and B37.7), and puncture related aneurysm (I72.0, I72.8, I72.9). Comorbidities were identified using the following ICD-codes: liver cirrhosis (K70.3, K71.7, K74.3, K74.4, K74.5, and K74.6), hepatic coagulopathy

(D68.4 and D68.8), hyperbilirubinemia (R17.0), chronic kidney disease (N18.1-N18.5), ascites (R18), and portal vein thrombosis (I81). In adition, the following clinical and demographical variables were evaluated: Sex, age, length of hospital stay, in-patient department, number of performed SIRTs per hospital, and federal state of treatment. In-hospital mortality was defined as the proportion of patients whose status of discharge was "death".

2.3. Statistical analysis

We performed all statistical analyses, through remote data access, at the Federal Statistical Office (DESTATIS; Wiesbaden, Germany) using the statistical program SPSS (IBM SPSS Statistics, Version 28.0 Armonk, NY: IBM Corp., USA) and the spreadsheet program Excel (Microsoft Corporation, Redmond, WA, USA). Cross tabulations were generated for the analysis of descriptive data. To assess differences in the frequency and type of SIRTs, different tumor types, duration of hospital stay, and in-hospital mortality, Welch's t-test and Fisher's exact test were applied. For the analysis of correlations Pearson's correlation coefficient was calculated. All statistical tests were two-sided and $P < 0.05$ was considered significant.

3. Results

3.1. Study population

During the observation period from 2012 to 2019, a total of 11,014 individual cases undergoing SIRT were identified (Table 1). The majority of patients were male (65%; Figure 1A and Table 1), and the sex ratio did not change during the observation period. The average age was 65 years (SD ± 11; Table 1 and Figure 1B). The mean length of hospital stay was 3.5 days (SD ± 1.9; Table 2). 71.7% ($n = 7{,}897$) of patients were discharged within 3 days. About 3.2% ($n = 355$) of patients stayed more than 7 days (Figure 1C).

We analyzed the patient collective in regard to relevant comorbidities, for example, liver cirrhosis (n = 1,324; 12%), chronic kidney disease ($n = 588$; 5.3%), ascites ($n = 168$; 1.5%), thrombosis of the portal vein ($n = 184$; 1.7%; Figure 1D), and in regard to the used radioisotope (Figure 2A and Table 2). The most common underlying disease was hepatic metastases of a primary extrahepatic tumor ($n = 5{,}974$; 54.3%). HCC was the second most common indication for SIRT ($n = 4{,}375$; 39.7%), while BTC contributed to 6% ($n = 665$) of cases (Figure 2B and C & Table 2). The mean number of SIRTs/year was 1,377 (SD ± 150). During the observation period, most SIRT interventions were performed in 2015 ($n = 1{,}587$). Individual cases increased steadily from 2012 to 2015 ($n = 1{,}177$ in 2012; $n = 1{,}587$ in 2015; +34.8%) and decreased in the following years with the lowest count of SIRTs performed in 2019 ($n = 1{,}150$; Figure 2C). There were changes within the spectrum of etiologies during the observational period with a trend in favor of HCC and BTC (proportion of HCC-SIRTs: 2012 34.3%; 2019: 43%, $P = 0.009$; mean: +1.2%/year; BTC-SIRTs: 2012: 5.1%, 2019: 8.4%, $P = 0.4$; mean: +0.5%/year). In contrast, the proportion of SIRT procedures due to hepatic metastases decreased significantly (2012: 60.6%; 2019: 48.6%, $P < 0.001$; mean: −1.7%/year; Figure 2C).

Table 1. Characteristics of the study population

Variable	Study population
Total number of SIRT procedures	11,014
Sex (total)	
Male (number and percentage)	7159 (65%)
Female (number and percentage)	3855 (35%)
Age (years; mean and SD)	65 (± 11)
Age group (total; number and percentage)	
<30 years	26 (0.2%)
30–40 years	222 (2%)
41–50 years	922 (8.4%)
51–60 years	2,468 (22.5%)
61–70 years	3,444 (31.4%)
71–80 years	3,293 (30%)
>80 years	608 (5.5%)
Federal State (total; number and percentage)	
Baden-Württemberg	1,184 (10.7%)
Bavaria	2,572 (23.4%)
Berlin	793 (7.2%)
Brandenburg	63 (0.6%)
Bremen	73 (0.7%)
Hamburg	199 (1.8%)
Hesse	358 (3.3%)
Mecklenburg-West Pomerania	95 (0.9%)
Lower Saxony	386 (3.5%)
Northrhine-Westphalia	2,332 (21.2%)
Rhineland Palatinate	225 (2%)
Saarland	181 (1.6%)
Saxony	820 (7.4%)
Saxony-Anhalt	1,084 (9.8%)
Schleswig Holstein	91 (0.8%)
Thuringia	558 (5.1%)

SIRT: Selective internal radiotherapy; SD: Standard deviation

3.2. Applied radioisotopes

The majority of SIRT procedures were performed with yttrium-90 (^{90}Y) ($n = 10{,}971$; 99.6%) over Holmium-166 (^{166}Ho) ($n = 43$; 0.4%; Figure 2A and Table 2). We did not record cases of ^{188}Re-SIRT. The first ^{166}Ho-SIRTs were recorded in 2017 and the number of ^{166}Ho-SIRTs increased through the years 2017 to 2019, despite overall being low, accounting for 2% of all SIRTs in 2019 ($n = 23$). By fitting a linear regression model describing the number of Holmium-SIRTs over time, the estimated slope was given by 7.3 treatments/year, indicating a significant increase in treatments from 2017 to 2019 ($P = 0.015$). There were significant differences in the mean length of hospital stay between ^{90}Y - (3.67 days, SD ± 2.0) and ^{166}Ho- (2.9 days, SD ± 1.3) based SIRTs (Table 2). Precisely, comparing the average duration of hospital stays between the two treatments resulted in significant differences for all 3 years 2017, 2018, and 2019, respectively, as the average differences were given by 0.59 days in 2017 ($P = 0.002$), 0.38 days in 2018 ($P < 0.001$), and 0.84 days in 2019 ($P = 0.005$).

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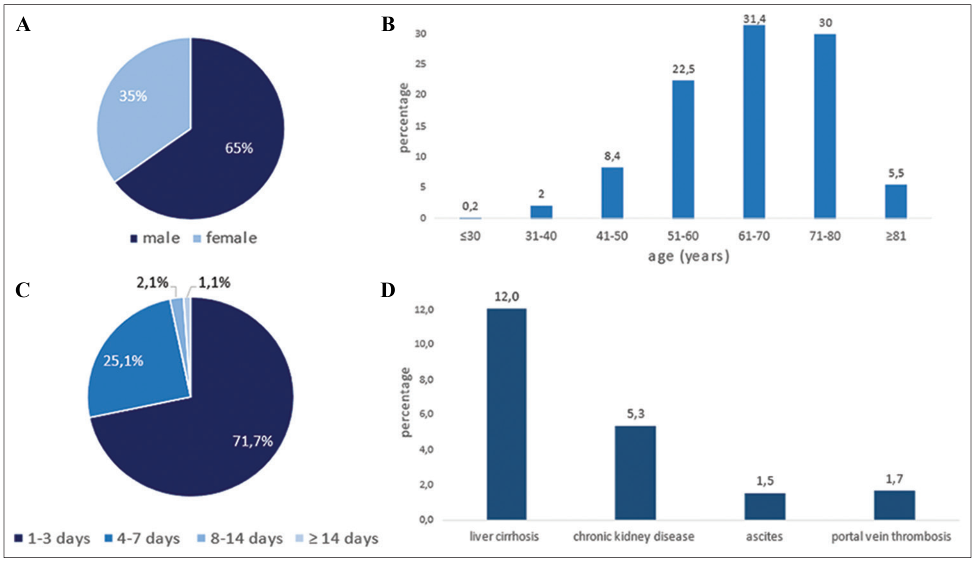

Figure 1. Patient-related aspects of performed selective internal radiotherapy (SIRTs) as a percentage of overall performed SIRTs. (A) Sex distribution. (B) Age distribution. (C) Length of hospital stay. (D) Comorbidities.

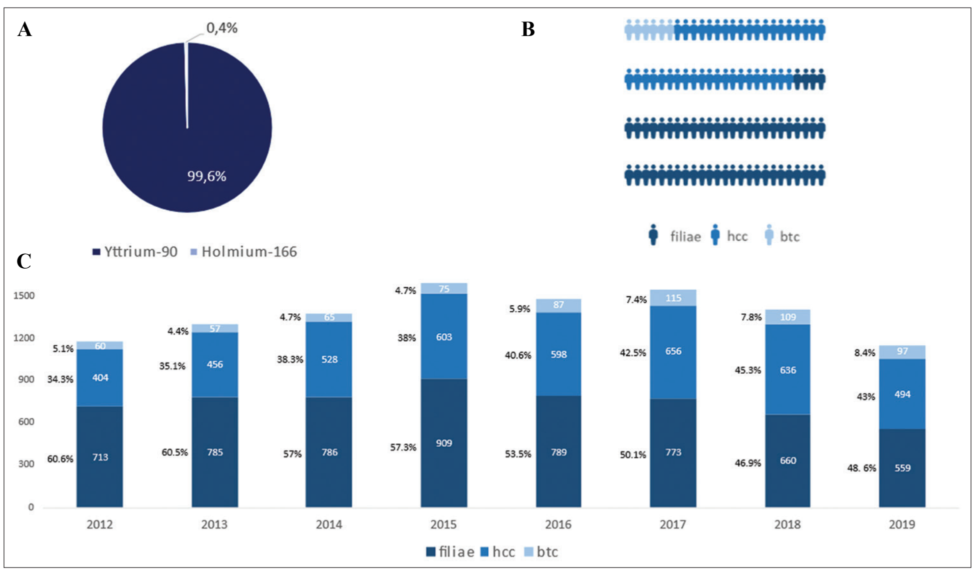

Figure 2. Current trends of selective internal radiotherapy (SIRT) in Germany. (A) Percentage of used radioisotopes (2012 – 2019). (B) Performed SIRTs related to the underlying entity; HCC: Hepatocellular Carcinoma, BTC: Bile tract cancer, Filiae: Liver metastasis; four lines each consisting of 25 figurines, one figurine representing one percent. (C) Total distribution of underlying diagnosis for SIRT between 2012 and 2019. Y-axis: Number of SIRTs; X-axis: Years. Within the bars: Number of SIRTs concerning the underlying diagnosis; Left of the bars: percentage of SIRT concerning underlying diagnosis and year.

3.3. In-hospital mortality and adverse events

The overall in-hospital mortality was 0.14% (*n* = 15; Figure 3A and Table 2). The overall complication rate was 3.9% (*n* = 431; Figure 3B and Table 2). The most common complications were gastrointestinal (ulcers, gastritis, and duodenitis) in 2.7% of all cases (*n* = 299; 69.4% of all recorded complications), followed by cholecystitis in 0.3% (*n* = 35; 8.1%), acute kidney injury in 0.3% (*n* = 32; 7.4%) and pulmonary events (pneumonia and pulmonary artery embolism) in 0.18% of all SIRT cases (*n* = 20; 4.6%). Further complications were sepsis in 0.17% (*n* = 19; 4.4%), pancreatitis in 0.08% (*n* = 9; 2.1%), acute liver failure in 0.05% (*n* = 6; 1.4%), and liver abscess in 0.04% (*n* = 4; 1%) of all cases. Catheter-related complications (aneurysm and major bleeding) occurred in 7 cases (0.06% of all cases; 1.6% of all complications; Table 2 and Figure 3B).

3.4. Regional distribution

Considering the regional geographical distribution in Germany, most SIRT cases were registered in Bavaria (*n* = 2,572; 23.4%). North Rhine-Westphalia contributed to 2,332 (21.2%) SIRTs, followed

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by Baden-Württemberg (n = 1,184; 10.7%). The lowest number of SIRT procedures was recorded in Brandenburg (n = 63; 0.6%; Table 1 and Figure 4A). Based on the population numbers, Saxony-Anhalt had by far the most SIRT procedures (61.1 SIRTs/year/1 million residents), followed by Berlin (27.1 SIRTs/year/1 million residents). Brandenburg (3.1 SIRTs/year/1 million residents) and Schleswig Holstein (3.9 SIRTs/year/1 million residents) recorded the lowest SIRT rates concerning the population (Figure 5A). The national average was 17.9 SIRTs/year/1 million residents (New Federal States and Berlin: 26.4; City States (Berlin, Bremen, Hamburg): 18.0; Old Federal States: 14.2; Figures 5A and B). A total of 482 hospitals did at least one SIRT between 2012 and 2019 (Table 2). The mean number of performed SIRTs/hospital during the observational period was 22.9 (SD ± 30.4) and ranged from a minimum of one SIRT (26 hospitals) to a maximum of 201 SIRTs (one hospital; Table 2). The 20 highest volume centers (>100 SIRTs) contributed to 25.6% (n = 2,818) of all SIRTs (Figure 4B).

Table 2. Characteristics of SIRT procedures, hospital distribution, tumor entities, and adverse events

Variable	Study population
Total number of SIRT procedures	11,014
^{90}Y (number, percentage)	10,971 (99.6%)
^{166}Ho (number, percentage)	43 (0.4%)
Hospital stay, days (total; SD)	3.5 (1.9)
^{90}Y (mean; SD)	3.7 (2.0)
^{166}Ho (mean; SD)	2.9 (1.3)
Number of performed SIRTs (2012–2019)	Hospitals, number (total number of SIRTs; percentage of all SIRTs)
0–25	349 (3343; 30.4%)
26–50	90 (3205; 29.1%)
51–75	15 (935; 8.5%)
76–100	7 (609; 5.5%)
>100	21 (2922; 26.5%)
Tumor entity (total)	
Hepatic filiae	5,974 (54.3%)
HCC	4,375 (39.7%)
BTC	665 (6%)
In-hospital mortality	15 (0.14%)
Adverse events (total; number and percentage)	
Gastritis	193 (1.8%)
Duodenitis	20 (0.2%)
Ulcus ventriculi	43 (0.4%)
Ulcus duodeni	43 (0.4%)
Acute cholecystitis	35 (0.3%)
Acute pancreatitis	9 (0.1%)
Acute kidney injury	32 (0.3%)
Sepsis	19 (0.2%)
Acute liver failure	6 (0.05%)
Liver abscess	4 (0.04%)
Aneurysm, major bleeding	7 (0.1%)

SIRT: Selective internal radiotherapy; SD: Standard deviation; HCC: Hepatocellular carcinoma; biliary tract cancer

4. Discussion

The most common underlying disease in our study was hepatic metastases of a primary extrahepatic tumor. HCC was the second most common indication for SIRT, while BTC contributed to a minor proportion of the cases. There were significant changes within the spectrum of etiologies during the observational period regarding HCC (mean: +1.2%/year) and filiae (mean: −1.7%/year). BTC (mean: +0.5%/year) tended to increase but the differences were not statistically significant. To the best of our knowledge, there is no published population- or geographical-based data about the distribution of SIRT in terms of different tumor entities.

Current guidelines mention SIRT in HCC patients with BCLC-0 as equally effective compared to TACE if ablation or surgical resection is not feasible in patients with solitary HCC ≤8 cm [14,15,23]. In patients with BCLC-A, SIRT could be considered in some patients as a bridge to resection or transplantation in larger tumors [23]. TACE, systemic therapy, and transplant in selected patients are the backbones for BCLC-B. SIRT can be indicated for intermediate (BCLC-B) or advanced-stage HCC patients who are poor candidates for TACE because of massive tumor size, bilobar disease, or portal vein thrombosis (PVT) [14]. The status of SIRT in patients with BCLC-C remains arguable after several studies (SAHaRA, SIRveNIB) comparing

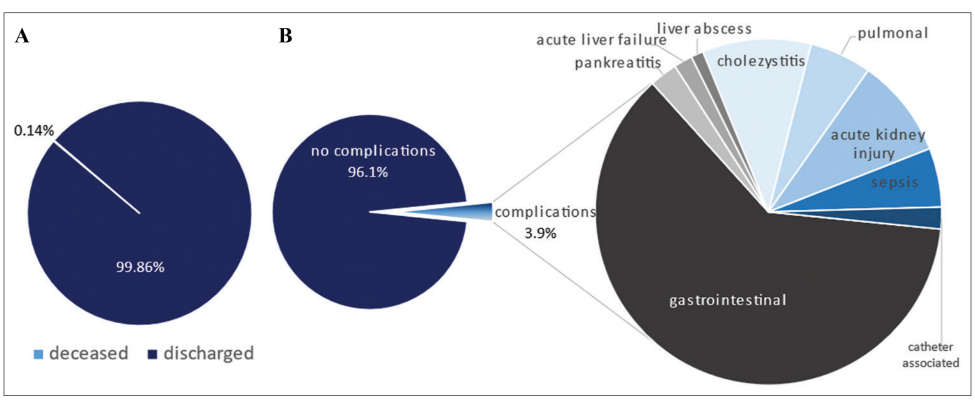

Figure 3. (A) Overall in-hospital mortality. (B) The proportion of complications concerning all performed selective internal radiotherapy procedures.

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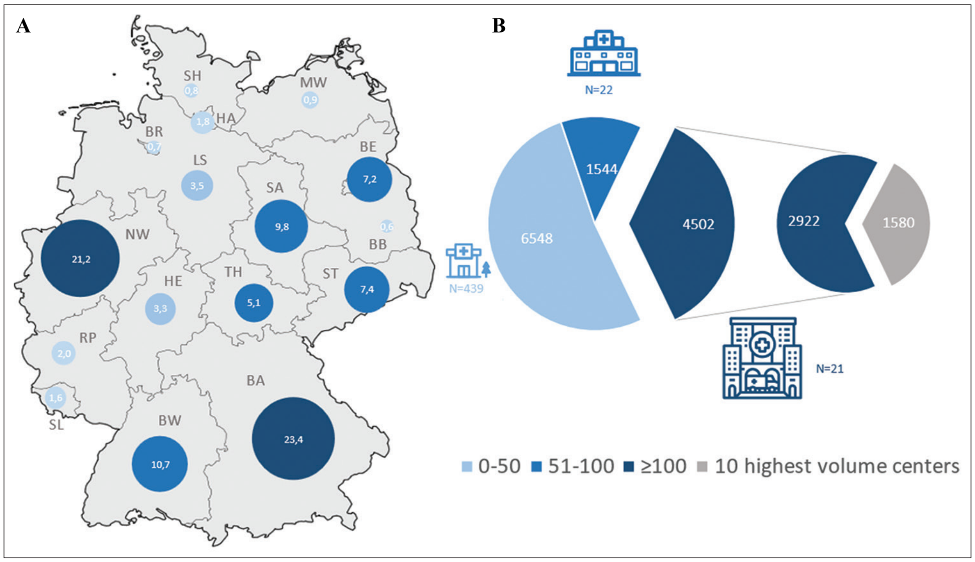

Figure 4. Regional distribution of selective internal radiotherapy (SIRT) in Germany. (A) Distribution of SIRT per federal state between 2012 and 2019 as percentage of overall performed SIRTs nationwide (n = 11,014 = 100%; very light blue: 0 – 3%; light blue: 3.1 – 5%; blue: 5.1 – 15%; dark blue: >15.1%); BB: Brandenburg, BE: Berlin, BW: Baden-Württemberg, BA: Bavaria, HE: Hesse, BR: Bremen, HA: Hamburg, MW: Mecklenburg-Western Pomerania, LS: Lower Saxony, NW: North Rhine-Westphalia, RP: Rhineland-Palatinate, SH: Schleswig-Holstein, SL: Saarland, SA: Saxony, ST: Saxony-Anhalt, TH: Thuringia. (B) Distribution of overall SIRTS (number) between 2012 and 2019 concerning the volume of the centers.

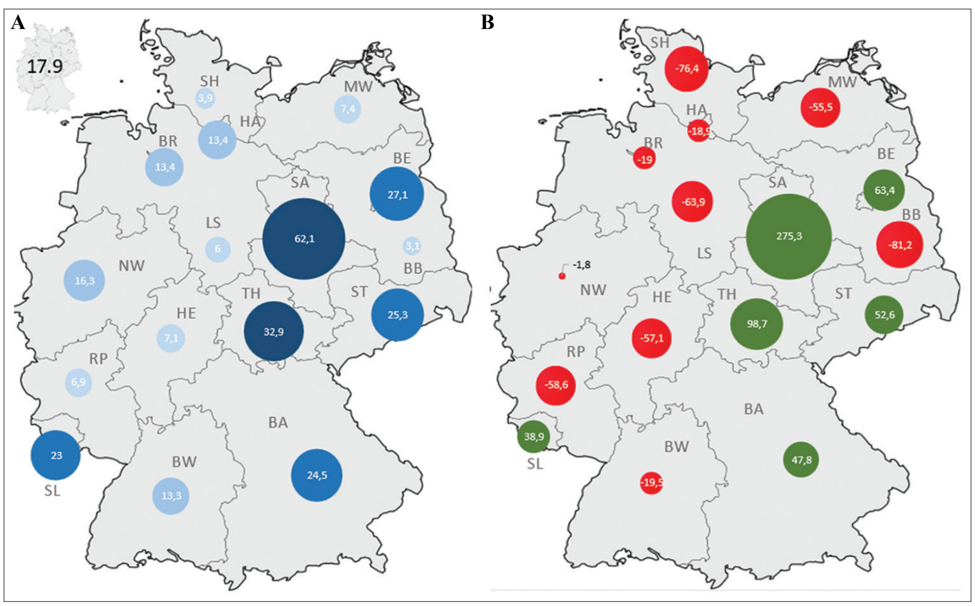

Figure 5. Population-based trends of selective internal radiotherapy (SIRT) in Germany. (A) SIRTs per one million residents per Federal State (very light blue: 0 – 10; light blue: 11 – 20; blue: 21 – 30; dark blue: >31); left top corner: nationwide average 2012 – 2019 (17.9). (B) Deviation (percentage) of performed SIRTs (number) in relation to nationwide average (green: +; red: -). BB: Brandenburg, BE: Berlin, BW: Baden-Württemberg, BA: Bavaria, HE: Hesse, BR: Bremen, HA: Hamburg, MW: Mecklenburg-Western Pomerania, LS: Lower Saxony, NW: North Rhine-Westphalia, RP: Rhineland-Palatinate, SH: Schleswig-Holstein, SL: Saarland, SA: Saxony, ST: Saxony-Anhalt, TH: Thuringia.

SIRT and former systemic first-line therapy (Sorafenib) failed to show survival benefit [24,25], especially against the background of newer promising systemic therapies. It is important to mention, that comparative data for SIRT vs. TACE in the context of HCC and BTC is generally low and based on small retrospective analyses showing a benefit in PFS and QoL for HCC patients but lacking a benefit in OS [26]. According to current guidelines, SIRT can be used (as well as other trans-arterial procedures, e.g., TACE) in liver-limited advanced cholangiocarcinoma if systemic therapies are not feasible or as an adjunct to systemic therapies and in locally limited intrahepatic cholangiocarcinoma in second-line therapy for selected patients [15-18]. The guideline recommendations regarding SIRT in HCC and BTC did not change essentially in recent years and the incidence of HCC in Germany did not change

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during the observational period [27], while the incidence of intrahepatic cholangiocarcinoma (ICC) is rising, but the overall incidence for BTC remained constant [9,18]. Given all that, the increasing number of SIRTs in the context of HCC and BTC in our study remains unclear. There was no disproportionate rate of PV in our cohort with only 1.7% (n = 184) which could explain the differences. However, it must be pointed out that we could not distinguish between the BCLC stages and the intention to treat (bridging/down-sizing vs. palliative setting) but the relatively high percentage of hospitals with a low number of SIRTs/year suggests the latter, at least in a relevant portion of the cohort.

A possible explanation for the decrease of performed SIRTs in hepatic metastases as of 2018 in our study is possibly attributable to the negative results of Phase III studies comparing a combination of chemotherapy +/- SIRT regarding OS and PFS [11].

Worldwide data on the use of the different radiation agents, and especially ^{166}Ho comparative data in different settings are missing. The vast majority of SIRT procedures in our study were performed with ^{90}Y (99.6%) over ^{166}Ho (0.4%). This finding is possibly due to the more recent approval of ^{166}Ho in Germany (in 2015) and the overall long-term experience of the centers in using yttrium-based SIRTs as the standard of care. The first ^{166}Ho-SIRTs in our study were recorded in 2017 and the number of ^{166}Ho-SIRTs increased significantly through the years 2017–2019, despite overall being low, accounting for 2% of all SIRTs in 2019. Comparing the average duration of hospital stay (^{90}Y: 3.67 days, ^{166}Ho: 2.9 days) between the two radioisotopes resulted in significant differences for each year. Despite large bio-physical differences (radiation activity, half-life-period), studies showed no difference in terms of OS and safety between the two available yttrium products (^{90}Y-resin vs. ^{90}Y -glass microspheres) or between ^{90}Y and ^{166}Ho [4-6,28-30]. Due to the comparatively low proportion of Holmium-based SIRTs and the overall low in-hospital mortality and low rate of adverse events in our study, we were not able to show differences in terms of mortality or adverse events between ^{90}Y- and ^{166}Ho-based SIRTs, but there were no cases of in-hospital mortality, ALF/ACLF, cholecystitis, ulcers ventriculi/duodenal, or lung artery embolism in the ^{166}Ho group. We have to state, that due to the low number of ^{166}Ho-based SIRTs in our study, these findings have to be re-evaluated in the future. Given all that, worldwide data about the use of different agents and comparative data between ^{90}Y- and ^{166}Ho-based SIRTs would be helpful.

Overall SIRT is a safe procedure with very low overall mortality with a well-definable spectrum of adverse events. The overall in hospital-mortality in our study was 0.14%. The reported treatment-related mortality rates are single-center experiences and mid-to-long-term SIRT-associated complications can occur weeks after the procedure, mostly after hospital discharge, ranging from 0% to 4% [31,32]. It should be emphasized that our study did not report the cause of death or long-term adverse events as we only were able to report the in-hospital course.

Despite being a minimal-invasive local therapy with the main effect based on the short range of radiation in the tumor tissue, a small amount of radiation is also delivered to the lungs (lung shunt). The procedure may only be performed if the expected lung shunt calculated based on the pretreatment planning does not exceed a certain threshold. Any other (non-pulmonary) extrahepatic, non-target deposition of microspheres is considered a complication and may result in substantial radiation-induced disease of the affected non-target organs. To avoid any extrahepatic and non-target deposition, thorough patient planning (including ^{99m}Tc-MAA-scanning respectively holmium scout dose) is mandatory before SIRT. Non-target complications may include radiation gastritis and gastrointestinal ulcers, cholecystitis, radiation pneumonitis, and radioembolization-induced liver disease (RAILD) which can lead to death and may occur despite thorough pretreatment planning [33]. The overall most common complication in our study was gastrointestinal (ulcers, gastritis, and duodenitis) in 2.7% of all cases. Gastrointestinal deposition of microspheres during the SIRT procedure due to the communication of liver arteries and the digestive tract through collaterals, reflux, or direct injection in close digestive arteries can lead to radiation ulcers and gastritis [34,35]. Ulcera ventriculi et duodeni occurred in each 0.4% of the cases, which is lower than the previously reported data: In the largest clinical trial on SIRT, the incidence of GI ulcers was 2.4% among patients with metastatic CRC [36]. A possible explanation for the lower rates in our study is the partially delayed onset of ulcers partially in a period of a few weeks and the comparatively short observational period in our study. Gastritis was the overall most frequent single complication with a total number of 193 cases (1.8% of all SIRTs). Duodenitis occurred in 20 cases (0.18% of all SIRTs). The overall cases are slightly higher but in line with the published data: Kennedy *et al.* reported a rate of 1% for gastritis [37]. More distal injections of microspheres can be performed to prevent these complications [38], but we did not record the rate of coil embolization or the exact localization of the injection.

Acute cholecystitis is a rare complication of SIRT. In an analysis of CT changes in the gallbladder following (20 – 30 days) SIRT, asymptomatic thickening and hyperenhancement of the gallbladder wall were observed in 10 out of 42 patients [39], but the rate of clinical apparent symptoms of acute cholecystitis is low and only about 10 cases of acute cholecystitis have been reported in the literature in detail [33,40]. Kennedy *et al.* [37] reported a rate of 1.3% (8 cases). In our study, there was a slightly lower rate of 0.3%.

Acute kidney injury occurred in 0.3% and pulmonary events (pneumonia and pulmonary artery embolism) in 0.2% of all performed cases. Further complications were sepsis in 0.17%, pancreatitis in 0.1%, and liver abscess in 0.04% of all cases. Catheter-related complications (aneurysm and major bleeding) occurred in 7 cases (0.06%). To the best of our knowledge, there are no published data about the frequency of these adverse events in a large patient cohort.

Acute liver failure (ALF) is a multifactorial process defined as loss of liver function that occurs rapidly usually with no pre-existing liver disease, unlike acute on chronic liver failure (ACLF) which requires underlying chronic liver disease (e.g., liver cirrhosis). SIRT may produce ALF/ACLF as well as subclinical liver injury: a significant and clinically irrelevant increase in total bilirubin after SIRT has been reported in different publications [41,42]. On the other hand, radioembolization-induced liver disease (REILD) is a sinusoidal obstruction syndrome and defined by the appearance of jaundice and ascites 4-8 weeks after SIRT in the absence of tumor progression or bile duct occlusion. In general, main liver complications do not result from the microembolic effect of SIRT but rather from radiation effects on the non-targeted liver tissue. Furthermore, radiation-induced blood vessel damage can result in clinically relevant liver toxicity after radioembolization in comparison with non-cirrhotic livers [43]. We recorded six cases (0.05%) of ALF/ACLF, which is lower than other reported data: Kennedy *et al*. reported 0.9%, and van Hazel *et al*. reported 1.3% in a combination arm with chemotherapy, both studies making no differences between ALF/ACLF and RAILD [36,37]. We did not record any REILD cases. This seems logically given the common onset of RAILD (4-8 weeks after SIRT) and the fact that only a small portion of patients (1.1%) in our study stayed hospitalized for more than 2 weeks after SIRT and there were no cases of hospitalization beyond 4 weeks. There were no cases of radiation pneumonitis in our study, which is in line with data from the literature [37] and can furthermore be attributed to the limited observational period (hospital stay) in our study. It must be pointed out that due to the retrospective database evaluation, we are unable to draw any causal link between the reported proportions and cannot exclude preexisting disorders or poor coding quality, but the reported frequencies are mostly in line compared to previously reported rates.

Population-based data about SIRT are largely lacking. During the observation period in our study, most SIRT interventions were performed in 2015. Individual cases increased steadily from 2012 to 2015 (mean increase per year: 10.5%) and decreased in the following years with the lowest count of SIRTs done in 2019. This finding can possibly be explained by increasingly strict assessment regarding cost coverage by the Medical Service of the Health Funds (MDK) in Germany and established alternative treatments (e.g., TACE) in most of the SIRT indications, but we are not able to prove this thesis. Based on the population numbers of the Federal States it is 19.7 times more likely to undergo SIRT in Saxony-Anhalt, compared to the federal state with the lowest rate, Brandenburg (Saxony-Anhalt: 61.1 SIRTs/year/1 million residents; Brandenburg: 3.1 SIRTs/year/1 million residents). These findings cannot be explained in terms of different regional tumor incidences (e.g., mean hepatic tumor (HCC + BTC)/100.000 residents 2012 – 2015 Saxony-Anhalt vs. Brandenburg: 8.1 vs. 7.7) [44]. The number of SIRTs performed in the New Federal States (26.4 SIRTs/year/1 million residents) was higher than in the Old Federal States (14.2), but the results were not statistically significant. Despite these mentioned large differences in the regional distribution, we could not identify structural or patient-related reasons for these findings: There was no correlation in terms of the overall population in the federal states, population density, number of university hospitals, average income, and the overall number of hospital beds. There was a correlation between the number of performed SIRTS and hospital beds per million residents (Pearson correlation coefficient: 0.43), as well as the mean average income (−0.4), but the results failed to show statistical significance. Other factors (e.g., local preferences and experience, different local availability and expertise), as well as historical reasons, may contribute to these findings.

We acknowledge some limitations of our study. First, it is a retrospective database evaluation and an epidemiological study unable to draw any causal link between performed SIRTs and the reported proportions. Furthermore, no information on coding quality in Germany is available and the database is not subject to systematic quality control between individual hospitals, which may lead to selection and analysis bias in this study. Nevertheless, it can be considered that endpoints such as liver failure and death are little or not influenced by coding errors and may correctly represent medical practice. Another limitation is that the analysis of cases/SIRT procedures does not include individual circumstances, which may contribute to the observed results. In addition, a larger sample size with standardized cases in each group and a longer follow-up duration would have been desirable. Finally, our data do not reveal important SIRT parameters such as dose of radiation, pretreatment/subsequent therapies, and treatment selectivity.

5. Conclusions

Overall SIRT is a safe procedure with very low overall in-hospital mortality (0.14%). It has a well-definable spectrum and a low rate of adverse events (3.9%). The resulting adverse events are mostly related to GI-tract side effects. Acute liver failure is a potentially fatal but exceptionally rare (0.05%) complication. The vast majority of SIRTS in Germany is performed with ^{90}Y (99.6%) but we observe an increasing number of ^{166}Ho-based SIRTS over the years. There are significant differences in the mean length of hospital stay between ^{90}Y- (3.67 days) and ^{166}Ho- (2.9 days) based SIRTs. Furthermore, we can show differences in the regional distribution of performed SIRT therapies and significant changes in the indications of SIRT over the years in favor of HCC and BTC. Despite large differences in the regional distribution and hospitals involved, we could not identify structural or patient-related reasons for these findings. Other factors (e.g., local preferences and experience, different availability and expertise) may contribute to these findings. In our opinion, there is a need for data to determine the role of SIRT in different entities and different settings (additive, sequentially) as well as prospective comparative long-term outcome results against newer systemic therapies and other established locoregional therapies. Furthermore, the promising beneficial bio-physical characteristics of Holmium-based SIRT should be further evaluated and a future two-arm study is needed to evaluate the potential side effects of each modality prospectively.

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Conflicts of Interest

The authors declared no conflict of interest.

Ethics Approval and Consent to Participate

The study was conducted according to the guidelines of the Declaration of Helsinki. Ethical review and approval were waived for this study because the database used for analysis contains anonymized electronic patient records. Patient data were analyzed in aggregated form without individual data being available. Participant consent was waived because this was a retrospective study and data were completely anonymized.

Availability of Data

The results of the remote data analyses provided by the Federal Statistical Office are available from the corresponding author on reasonable request.

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