

Selective Internal Radiotherapy in Germany: a review of indications and hospital mortality from 2012 to 2019

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The first time.. the first study ect ect"

Figures and table

Figure 5, please add legend for the colors

Tables need to be restyled since they are difficult to read

Reviewer #6: This article systematically analyzes the state of Selective Internal Radiotherapy (SIRT) in Germany based on standardized hospital discharge data from 2012 to 2019. It covers indications, hospital mortality, adverse events, and trends in SIRT use in Germany. The study found that SIRT is a safe procedure, with low in-hospital mortality and a well-defined spectrum of adverse events. The most common indication for SIRT was hepatic metastases, and yttrium-90 was the most commonly used beta-radiator. The study also reports differences in the regional distribution of performed SIRTs and changes in the indications and radiators used over seven years. Although the study is original, it is more like an epidemiological cross-sectional study, given the sample size and limitations.

Title

The title conveys the study's intentions but could be more concise. The following title is suggested: "Selective Internal Radiotherapy (SIRT) in Germany: A Review of Indications and Hospital Mortality from 2012 to 2019."

Abstract

The abstract provides a concise and lucid overview of the objectives, main methodologies, significant outcomes, and concluding remarks. It contains sufficient information and avoids extraneous details.

Introduction

The introduction outlines the present status of the subject, acknowledges existing limitations, elucidates the rationale behind the research, and defines the study's objective and research question.

Methods

The patient eligibility criteria and variables are clearly defined, including the specific treatment approach (SIRT), OPS and ICD codes, and comorbidities. In-hospital mortality is defined as the proportion of patients discharged with the status of "death." The statistical analysis includes Welch's t-test and Fisher's exact test, Pearson's correlation coefficient, and a p-value <0.05 is considered significant. The study's main limitation is that it is based on retrospective data and cannot control for all potential confounding factors. The absence of additional ethics approval due to the complete anonymization of patient information may also raise some concerns. The study included all patients meeting the inclusion criteria, and the exclusion criteria were not applicable. The authors did not classify the use of different β -radiators of SIRT for indications separately, and the significant difference in the number of study groups may lead to bias and should not be disregarded.

Results

The findings presented are consistent with the methods and data described in the text and accurately depicted in the figures and tables. The extra information regarding the number of various SIRTs each year appears to be irrelevant.

Discussion and Conclusion

The first paragraph of the discussion section appears to be more like a result and requires the author's consideration. The authors provide a clear explanation of their findings and make comparisons with other research in the field. However, it is unclear whether they followed the recommended procedures as outlined in the guidelines. The study discusses the use of SIRT in various stages of HCC, but it does not specify which guidelines were followed for each case. Although the study has mentioned its limitations, it should have explicitly stated that it is a retrospective epidemiological study. Additionally, the study requires a larger sample size with standardized cases in each group and a longer follow-up duration. A future two-arm study is needed to evaluate the potential side effects of each modality prospectively. The conclusion should be concise and to the point, outlining the key findings and their implications. The first four lines of the conclusion section are unnecessary, and the entire conclusion section reads more like a summary of the discussion.

Authors' response

Reviewer #1:

The reviewer honours the amount of data analyzed and the work behind such a retrospective cohort study. Whether the data gathered leads to clinically relevant results remains to a certain extent open. A well-written manuscript with neat graphs. Following

minor changes are recommended:

We would like to thank this reviewer for her/his positive statement on our study. Following these minor revisions of our manuscript, we hope that our study will be further considered for publication in the JCTR.

1. The headline is misleading. 2021 until 2019 is not current. Please rephrase.

You are right, we rephrased the headline

2. For a double blinded review process the authors might not indicate their institution in line 25. Please rewrite... "University Hospital Duesseldorf"

We thank the reviewer for this comment. As far as we are concerned, we believed that it is necessary to indicate authorship, affiliations and correspondence upon submission. However, we agree to have this information removed by the editor if he or she wishes to do so.

3. Due to the nature of the study, one might expect a more extensive discussion in terms of selection and measurement bias in this study as well as description of identified confounders and methods used for controlling for confounding during analysis. Please elaborate accordingly.

This is a very relevant comment and we would like to thank this reviewer. We therefore amended

our manuscript and discussed the limitations of the study more extensively (see page 16, lines 8-19).

Reviewer #2:

In the absence of an appropriate databank, is being used an interesting strategy to provide large-scale data (over 11.000 procedures) on the development and perioperative/acute outcomes of SIRTs in Germany. As the authors also point out, an important limitation in searching for patients and side-effects through DRG-system is the lack of correlation with the quality and accuracy of the coding in Germany, which may lead to a possible bias on health economic grounds. It would also be interesting to have access to further data on side effects, such as those arising after hospital discharges. The text seems well written, the grammar and language of the article are suitable. The data (with the limitations) are well presented.

We would like to thank reviewer #2 for her/his favorable feedback and positive assessment of our study. Indeed, longer follow-up and access to data after discharge (especially relating to (delayed) adverse events) would be interesting and this is clearly a disadvantage of using the DRG system.

Reviewer #3:

This paper evaluates in a large cohort the adverse events of SIRT at the time of the treatment. Nevertheless toxicity related to SIRT arrives weeks or months after SIRT due to radiation (REILD, ulcers, pneumonitis....). These adverse events are not taken into account in this study. Only the toxicity related to the arteriography (embolization effect, organ ischemia, toxicity related to contrast) are evaluated at the time of the procedure and they are not representative of the common side effects related to SIRT. A second problem occurs in the comparison between 166 Ho microspheres and 90 Y microspheres. This study seems demonstrate longer hospitalization using 90Y microspheres with a mean length of hospital stay of more 3 days. This result is very curious, generally patients don't stay more than 24hours. Maybe the workup with the simulation of SIRT using Tc 99m- MAA was performed in the same hospitalization just before the treatment, it is often the case using SIR-Spheres in Germany.

We would like to thank reviewer #3 for her/his feedback and the very interesting comments and would like to answer in detail the minor comments: as mentioned above, the comparatively

short observation period of each case (limited to the in-hospital course) is a restriction of our data. Furthermore, we cannot rule out Tc99m MAA in the same hospitalization, but the DRG system in Germany limits the hospital stay (under economic criteria) between 1 (minimum length of stay) and 7 days (maximum length of stay), which fulfill 97.2% of the performed procedures in our study (10,659/10,970). 72% of the patients were discharged within 3 days. Given that, the mean hospital stay of 3.8 days in our study is economically effective for the hospitals. Another interesting point in this context would be the length of hospital stay in regard to the number of performed procedures per year per hospital, but we did not capture this data.

Regarding minor comments

- 166 Ho microspheres arrived later in the market, had the EU approval only few years ago, explaining why this treatment was performed in only a few percentage in this large serie.

We would like to thank this referee for the important comment, we added this point (see page 4, line 15).

- Glass and resin microspheres don't differ significantly by their diameter, they differ mainly by the number of injected particles and by the activity per microsphere

Thank you, we clarified that (see page 12, line 21).

Reviewer #5: Overall comment

The study is interesting but the manuscript need major editing. There are many sentences not supported by either publications or clinical practice. Overall, English needs to be improved

We would like to thank this reviewer for her/his positive statement on our study and the highly relevant and very constructive comments posed by this referee. By addressing all points raised

by this reviewer, we were able to significantly increase the quality and focus of our manuscript. Following this major revision of our manuscript, we hope that our study will be further considered for publication.

Moreover, it would be useful to put Tables and figures in parenthesis when cited in the text, to be more comprehensible.

We put the terms „tables“ and „figures“ in parentheses in the all sections.

The term "radiators" is unusual, please change with radioisotope

We substituted the term „radiators“ with „radioisotope“ in the whole text.

Overall discussion as well as introduction and conclusion are too long

We thank reviewer #5 for the important advice. We have cut the introduction and the conclusion back considerably – we are sure, this will clarify the statements of our study.

Page 4 line 41: please write RCT in full since it is the first time acronym appears; also delete "generally" from the sentence.

We corrected this (see page 4 line 20 and line 21).

Page 4 lines 48-54: references are needed; also modify the term "preferentially tumor effect" since it is ambiguous

We added references and corrected the term „preferentially tumor effect“ into „predominantly effect on tumor tissue compared to liver parenchyma” to make this point more accurate (see page 4 line 23 and line 27).

Page 5 lines 3-11: this sentence is not connected to the previous one. Page 5 lines 13-27: this paragraph is very confusing, please edit. Moreover, the sentence "SIRT is one of the transarterial therapies predominantly used in the non-curative setting" needs to be supported by published data (I don't think it is actually so widely used worldwide)

We thank the reviewer for this important note. We rewrote this part completely to avoid, that it could be misunderstood (page 5, lines 5-17).

Page 5 lines 33-44: the guidelines in HCC differ a lot when it comes to indications to SIRT; please be more precise. Page 6 lines 46-56: again, be more precise when describing indications to SIRT, at least according to guidelines. Otherwise, specify that this is clinical practice

These are indeed highly relevant comments. We added the ESMO- and EASL-guidelines for HCC regarding SIRT as well as the ESMO-guidelines for cholangiocarcinoma. Furthermore we clarified, that SIRT for hepatic metastases of primarily extrahepatic tumors is clinical practice (page 5, lines 19-26; page 6 lines 1-3).

Page 6 line 6: no need to specify Results

We removed this specification.

Page 8 lines 47-58: since the number of procedures performed with holmium is so low compared to Y90, I would avoid any comparison also because I assume that only one or two centers are performing Ho-SIRT and probably the differences in hospital stay are more

related to internal policies.

We thank the reviewer for this important comment. We did not record the number of centers which performed Ho-SIRTS, so we can not rule out a potential bias here. Furthermore, due to the overall comparatively small number of Ho-SIRTS in our study, our results have to be interpreted with appropriate restrictions. A point we clarified (page 12, line 28 und page 13 line 1).

Please divide the paragraph "outcome and geographical distribution" into two different section. Rename "outcome" since it is too generic and it actually refers only to periprocedural/inhospital complications

We divided this paragraph into two different sections. This will improve the legibility of the section. We thank the reviewer for this reference.

Page 9 line 52: if the maximum number of SIRT was 201 for one center over 7 years period, that means less than 30 procedures / year. Authors should give a sort of threshold to define a "high-volume center" on the basis of number of procedures / year and provide number of "high volume centers" accordingly

We thank the reviewer for this note. We supplemented the threshold for high volume centers (>100 SIRTS over the observational period), page 10, line 6.

Discussion

Avoid to repeat sentences already present in the introduction and too many data already given in the results.

We removed results, which were given before, particularly where they are not discussed in detail in this section (see page 11 lines 4-5).

The changes in indications is not so strange, considering the data published on metastasis in 2017; this should be discussed

A very important note, that we have implemented by discussing this aspect against the background of the negative results of the FOXFIRE, SIRFLOX, and FOXFIRE studies (see page 12, lines 9-11).

Also, indications for SIRT could be related to reimbursement policies; please describe if and how these have changed over the years. Avoid comparison between Y and HO, since the data are too scarce today

This is an interesting point. Of course, we cannot rule out possible changes in reimbursement policies over time, since no systematic data about this policy is available and especially given the fact, that our study is a nationwide epidemiological study and the Health Insurance Funds and/or the Medical Service of the Health Funds have potentially different regional reimbursement strategies. This may have let clinicians' favour (or not favor) SIRT-therapies in individual cases. This may particularly be the case, if other therapies are available and in label – a situation that is frequently given for SIRT (in a comparative field, e.g. TACE), but this remains speculative.

Page 14 first line: radiation pneumonitis cannot be identified early after treatment, probably this is the reason why no cases were registered

We have emphasized this, page 15 line 9.

Avoid sentences such as "this is the first time.. the first study ect".

We deleted these phrases.

Figures and table

Figure 5, please add legend for the colors

We added a legend for Figure 4 and 5 (see page 20, line 3, and page 21, line 2).

Tables need to be restyled since they are difficult to read

At this point, we do not agree. In our opinion, the tables have a clear layout.

Reviewer #6

This article systematically analyzes the state of Selective Internal Radiotherapy (SIRT) in Germany based on standardized hospital discharge data from 2012 to 2019. It covers indications, hospital mortality, adverse events, and trends in SIRT use in Germany. The study found that SIRT is a safe procedure, with low in-hospital mortality and a well-defined spectrum of adverse events. The most common indication for SIRT was hepatic metastases, and yttrium-90 was the most commonly used beta-radiator. The study also reports differences in the regional distribution of performed SIRTs and changes in the indications and radiators used over seven years. Although the study is original, it is more like an epidemiological cross-sectional study, given the sample size and limitations.

Title

The title conveys the study's intentions but could be more concise. The following title is suggested: "Selective Internal Radiotherapy (SIRT) in Germany: A Review of Indications and Hospital Mortality from 2012 to 2019."

We thank reviewer #6 for the detailed notes. We reframed the title in favor of the suggested term.

Abstract

The abstract provides a concise and lucid overview of the objectives, main methodologies, significant outcomes, and concluding remarks. It contains sufficient information and avoids extraneous details.

Introduction The introduction outlines the present status of the subject, acknowledges existing limitations, elucidates the rationale behind the research, and defines the study's objective and research question.

We would like to thank the reviewer for her/his positive statement on our abstract.

Methods

The patient eligibility criteria and variables are clearly defined, including the specific treatment approach (SIRT), OPS and ICD codes, and comorbidities. In-hospital mortality is defined as the proportion of patients discharged with the status of "death." The statistical analysis includes Welch's t-test and Fisher's exact test, Pearson's correlation coefficient, and a p-value <0.05 is considered significant. The study's main limitation is that it is based on retrospective data and cannot control for all potential confounding factors. The absence of additional ethics approval due to the complete anonymization of patient information may also raise some concerns. The study included all patients meeting the inclusion criteria, and the exclusion criteria were not applicable. The authors did not classify the use of different β -radiators of SIRT for indications separately, and the significant difference in the number of study groups may lead to bias and should not be disregarded.

This is a very important comment of the reviewer. Due to the overall low number of Ho-SIRTs in our study, we did not perform sub-group analyses regarding some key aspects (e.g. indication). This is an important limitation, which we highlighted to a greater extent (see page 12 line, 28, and page 13, line 1).

Results

The findings presented are consistent with the methods and data described in the text and

accurately depicted in the figures and tables. The extra information regarding the number of various SIRTs each year appears to be irrelevant.

We would like to thank the reviewer for her/his positive statement on our results section.

Discussion and Conclusion

The first paragraph of the discussion section appears to be more like a result and requires the author's consideration.

You are right, we clarified that, see page 11, lines 3-10.

The authors provide a clear explanation of their findings and make comparisons with other research in the field. However, it is unclear whether they followed the recommended procedures as outlined in the guidelines. The study discusses the use of SIRT in various stages of HCC, but it does not specify which guidelines were followed for each case.

You are right again, and we cannot rule out occasional SIRT therapies on an individual therapy decision in some cases, but we assume that current European and German guidelines (ESMO/EASL/S3-guideline) were applied at least at the vast majority of the cases, especially with regard to in label use of the radioisotopes and/or the SIRT-procedure itself.

Although the study has mentioned its limitations, it should have explicitly stated that it is a retrospective epidemiological study. Additionally, the study requires a larger sample size with standardized cases in each group and a longer follow-up duration. A future two-arm study is needed to evaluate the potential side effects of each modality prospectively. The conclusion should be concise and to the point, outlining the key findings and their implications. The first four lines of the conclusion section are unnecessary, and the entire conclusion section reads more like a summary of the discussion.

We thank this reviewer for this interesting and relevant note. We added this point (see page 16, lines 8-19). Furthermore, we removed the first four lines of the conclusion.

2nd Editorial decision
15-Mar-2023

Ref.: Ms. No. JCTRes-D-23-00018R1
Current Developments of Selective Internal Radiotherapy (SIRT) in Germany: A Systematic Analysis of Indication and Hospital Mortality between 2012 and 2019
Journal of Clinical and Translational Research

Dear authors,

I am pleased to inform you that your manuscript has been accepted for publication in the Journal of Clinical and Translational Research.

You will receive the proofs of your article shortly, which we kindly ask you to thoroughly review for any errors.

Please notify our assistant editor/production editor when you receive the proofs if your article should belong to a special issue specifying the issue's title.

Thank you for submitting your work to JCTR.

Kindest regards,

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Comments from the editors and reviewers: