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HDR brachytherapy versus robotic-based and linac-based stereotactic ablative body radiotherapy in the treatment of liver metastases – A dosimetric comparison study of three radioablative techniques

Mateusz Bilski [a,b,c,1], Katarzyna Korab [d,2], Małgorzata Stąpór-Fudzińska [e,3], Julia Ponikowska [d,4], Agnieszka Brzozowska [f,5], Łukasz Sroka [e,6], Ewa Wojtyna [d,7], Sylwia Sroka [d,8], Marta Szlag [e,9], Paweł Cisek [a,b,10], Aleksandra Napieralska [g,*,11]

[a] Radiotherapy Department, Medical University of Lublin, Lublin, Poland
[b] Brachytherapy Department, Saint John's Cancer Center, Lublin, Poland
[c] Radiotherapy Department, Saint John's Cancer Center, Lublin, Poland
[d] Department of Medical Physics, Saint John's Cancer Center, Lublin, Poland
[e] Radiotherapy Planning Department, Maria Skłodowska-Curie National Research Institute of Oncology Gliwice Branch, Gliwice, Poland
[f] Department of Medical Mathematics and Statistics with e-Health Laboratory, Medical University of Lublin, Lublin, Poland
[g] Radiotherapy Department, Maria Skłodowska-Curie National Research Institute of Oncology in Gliwice and Kraków, Poland

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ABSTRACT

Purpose: The aim of our study was to compare dosimetric aspects of three radioablation modalities – direct high-dose-rate brachytherapy (HDR-BT) and virtually planned stereotactic body radiation therapy performed on CyberKnife (SBRTck) and Elekta Versa HD LINAC (SBRTe) applied in patients with liver metastases.

Material and methods: We selected 30 patients with liver metastases, who received liver interstitial HDR-BT and virtually prepared plans for SBRTck and SBRTe. In all the cases, the prescribed dose was a single fraction of 25 Gy. Treatment delivery time, doses delivered to PTV and organs at risk, as well as conformity indices, were calculated and compared.

Results: The longest median treatment delivery time was observed in SBRTck in contrast to HDR-BT and SBRTe which were significantly shorter and comparable. HDR-BT plans achieved better coverage of PTV (except for D98%) in contrast to SBRT modalities. Between both SBRT modalities, SBRTck plans resulted in better dose coverage in Dmean, D50%, and D90% values compared to SBRTe without difference in D98%. The SBRTe was the most advantageous considering the PCI and R100%. SBRTck plans achieved the best HI, while R50% value was comparable between SBRTe and SBRTck. The lowest median doses delivered to uninvolved liver volume (V5Gy, V9.1Gy) were achieved with HDR-BT, while the difference between SBRT modalities was insignificant.

* Corresponding author at: Radiotherapy Department, Maria Skłodowska-Curie National Research Institute of Oncology in Gliwice and Kraków, Ul. Wybrzeze AK 15, 44-100 Gliwice, Poland.

E-mail addresses: bilskimat@gmail.com (M. Bilski), korabkatarzyna@gmail.com (K. Korab), malgorzata.stapor-fudzinska@gliwice.nio.gov.pl (M. Stąpór-Fudzińska), ponikowska.julia@gmail.com (J. Ponikowska), agnieszkabrzozowska@umlub.pl (A. Brzozowska), lukasz.sroka@gliwice.nio.gov.pl (Ł. Sroka), ewaa.wojtyna@gmail.com (E. Wojtyna), sylwia.sroka94@gmail.com (S. Sroka), marta.szlag@io.gliwice.pl (M. Szlag), pcisek@interia.eu (P. Cisek), aleksandra.napieralska@io.gliwice.pl (A. Napieralska).

[1] ORCID: 0000-0002-4962-3028.
[2] ORCID: 0009-0007-0201-7956.
[3] ORCID: 0000-0003-2668-2022.
[4] ORCID: 0009-0005-3300-9073.
[5] ORCID: 0000-0001-5553-1122.
[6] ORCID: 0000-0003-1960-3605.
[7] ORCID: 0009-0003-6376-1886.
[8] ORCID: 0009-0007-4477-412X.
[9] ORCID: 0000-0002-4279-1934.
[10] ORCID: 0000-0001-8375-5289.
[11] ORCID: 0000-0002-7390-9165.

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SBRT plans were better regarding more favourable dose distribution in the duodenum and right kidney, while HDR-BT achieved lower doses in the stomach, heart, great vessels, ribs, skin and spinal cord. There were no significant differences in bowel and biliary tract dose distribution between all selected modalities.
Conclusions: HDR-BT resulted in more favourable dose distribution within PTVs and lower doses in organs at risk, which suggests that this treatment modality could be regarded as an alternative to other local ablative therapies in carefully selected patients' with liver malignancies. Future studies should further address the issue of comparing treatment modalities in different liver locations and clinical scenarios.

Background

The treatment of unresectable liver metastases is challenging, and there is a wide range of effective local treatment options available, such as radiofrequency ablation (RFA) or microwave ablation. Recently, radiation-based therapies have evolved as an alternative or multimodal treatment, and stereotactic body radiation therapy (SBRT) is currently regarded as one of the local therapies for patients with inoperable liver tumours or liver metastases [1,2]. Due to the integration of new planning software and improvements in image guidance and radiation delivery, SBRT can be safely delivered with curative doses. Recently published meta-analyses proved the efficacy and safety of such an approach [3–6]. The total dose prescribed is usually between 30 and 50 Gy in three to five fractions; however, no consensus regarding optimal dosing was reached [3]. Both, gantry-based and robotic-based SBRT are acceptable as treatment delivery options, and prior fiducial implantation is strongly advised [7,8]. Furthermore, for target volume motion management, a dedicated 4D-CT with contrast is essential, and abdominal compression or respiratory gating is often required.

Another alternative for local ablative treatment of liver malignancies is interstitial high-dose-rate brachytherapy (HDR-BT). The results, published so far, showed comparable rates of local control of liver lesions among HDR-BT, SBRT and radiofrequency ablation. Therefore, HDR-BT was included as one of the treatment options for early-stage hepatocellular carcinoma in the European Society for Medical Oncology (ESMO) guidelines [2,9,10].

In the era of oligometastatic disease (OMD), new targeted therapies and immunotherapeutic drugs, metastatic directed therapy (MDT), have the possibility of prolonging the overall survival (OS) and/or progression-free survival (PFS) of those patients [11,12]. It is becoming crucial to select the optimal MDT modality to achieve local control (LC) of the tumour while limiting the dose to organs at risk as much as possible. More popular clinical scenarios in those patients involve subsequent courses of MDT in a reirradiation setting [13]. So far, only a few studies comparing the SBRT and HDR-BT for liver lesions have been published in the context of primary planning.

The objective of our study was to compare the features of three radiation-based local treatments: robotic-based CyberKnife SBRT (SBRTck), gantry-based LINAC based SBRT performed on an Electa Versa HD accelerator (SBRTe) and HDR-BT. The aim of the present study was to assess detailed insights into the dose exposure of organs at risk (OAR) and to compare dose coverage between three selected radiotherapy modalities. Our results may help in choosing one of those MDT radiotherapy-based techniques in the treatment of patients with liver metastases not based on patient-related factors but on the planning-based factors.

Material and methods

We conducted a dosimetry comparison study between actually performed interstitial HDR-BT and virtually planned SBRT on the CyberKnife (SBRTck) and Elekta Versa HD Linear Accelerator (SBRTe). For the purpose of this analysis, we selected 30 patients with liver metastases, who received liver interstitial HDR-BT at the St. John's Cancer Center in Lublin (Poland) between 2017 and 2023. Patients suitable for HDR-BT must meet the criteria: good performance status (WHO <3), tumour diameter below 10 cm, number of metastases ≤ 5, technical possibilities of application of catheters (lack of large vessels in close proximity to the lesions), creatine level below 2 mg/dl, haemoglobin > 8 mg/dl, white blood cells >2000/mm^3, neutrophils >1500/mm^3, platelets >50,000/mm^3, INR <1.5, liver enzymes < 2.5 upper normal limit. Patients who don't meet those criteria, as well as those with target in close proximity of large vessels or with other OARs close to the target, which prevents the achievement of the planned dose without compromising of doses delivered to OARs, and those with any form of inflammation inside the abdominal cavity, were excluded and not offered HDR-BT. Metastases with an upper diameter of 4 cm were chosen for the purpose of this analysis. Location or histopathological subtype were not criteria for inclusion in the study. All patients had a plan prepared with a single fraction of 25 Gy. The study was performed in accordance with the Declaration of Helsinki in its latest version and was approved by the Ethics Committee of the Lublin Medical Chamber (Lublin, Poland) (approval no. LIL-KB-20/2014). Due to the retrospective nature of the study, written informed consent from patients was not required. For this dose-planning study, all patient data were utterly anonymized in an irreversible manner, and no clinical follow-up data were obtained.

Interstitial HDR brachytherapy – application and planning

The general brachytherapy procedure applied in Lublin was described previously by our group [14,15]. Applicators (200 mm or 320 mm long) were placed under general anaesthesia and under the control of a 32-slice computed tomography (CT) scanner with real-time fluoroscopic imaging. After applicator insertion, a CT scan was acquired with a slice thickness of 1.5–3 mm with and without contrast. Radiation oncologist (RO) delineated the clinical target volume for brachytherapy (CTVbt) using planning CT (with and without contrast) and, if needed, registered it with diagnostic magnetic resonance imaging (MRI) and/or positron emission tomography (PET/CT). No additional margin was applied, so for this analysis, BT CTV is the same as BT PTV (PTVbt). Organs at risk (OARs), were also delineated by RO. The source step was set to 5 mm. In most cases, dose volume optimization was performed using inverse planning as a starting point for manual optimization. All patients were planned in the BrachyVision planning system version 10 or 16; (Varian Medical Systems, Inc.). The TG-43 algorithm was used for dose calculations. Treatment plans were delivered with BRAVOS or GammaMed iX HDR iridium 192 after loaders (Palo Alto, USA). The dose constraints for OARs are presented in Table 1 [16–20]. The treatment delivery time in brachytherapy varies depending on the current activity of the radioactive source. To be able to compare the irradiation times, they were given a nominal source value of 10 Ci. Application and planning times are not included, as they depend on many components, such as the experience of the radiation oncologist and medical physicist, the number of applicators, and the difficulty of the plan.

SBRT general planning rules

Using planning CT datasets acquired for HDR-BT, a total number of 30 treatment plans have been prepared for both SBRT modalities. Planning treatment volume (PTV) was defined as CTV + 5 mm margin in each direction for SBRTck and SBRTe.

Table 1
Dose constraints for organs at risk (OARs) used for all three selected radiotherapy modalities.

Organ	Dose (D) or volume (V) constrains
Uninvolved Liver	V9.1 Gy < 700 cc V10Gy < 700 cc D66%<10 Gy
Spinal Canal	Dmax < 14 Gy D0.35 cc < 10 Gy D1.2 cc < 7 Gy D1cc < 14 Gy
Biliary tract	Dmax < 25 Gy
Bowel	Dmax < 15.4 Gy D5cc < 11.9 Gy
Skin	Dmax < 26 Gy D10cc < 23 Gy
Gallbladder	Dmax < 20 Gy
Great Vessels	D1cc < 27 Gy
Ribs	Dmax < 30 Gy D1cc < 23 Gy
Heart	Dmax < 22 Gy
Kidney (Right)	D1cc < 18 Gy Dmean < 6 Gy D100cc < 9.5 Gy
Duodenum	Dmax < 12.4 Gy D5cc < 11.2 Gy D10cc < 9 Gy D1cc < 15 Gy
Stomach	Dmax < 12.4 Gy D10cc < 11.2 Gy D1cc < 15 Gy
Esophagus	Dmax < 24 Gy D1cc < 15 Gy

Virtual CK SBRT treatment planning

Treatment plans have been prepared in the Precision CyberKnife System. The MLC collimator and Fiducial Respiratory tracking method were selected. Each treatment plan was optimized for PTV while maintaining tolerance doses for organs at risk. Time and beam reduction were performed before the final dose calculation. Dose normalization in the CyberKnife system is to the reference isodose, which is 80 % by default (can be modified). Irradiation time was estimated by adding 15 min for patient positioning and a verification image every 60 s. Dose prescribed was 25 Gy in one fraction like in HDR-BT. Treatment planning for CK SBRT and LINAC SBRT was optimised for PTV while maintaining tolerance doses for organs at risk. The dose constraints for OARs are given in Table 1.

Virtual Elekta Versa HD LINAC SBRT treatment planning

Using the same CT datasets, plans were made for the Elekta Versa HD linear accelerator with the MLC (Multileaf Collimator) Agility. PTV margin is used, for liver metastasis SBRT planning, with the ABC (Active Breathing Coordinator) breathing control system; (Elekta). On the RayStation Planning system, plans based on the VMAT (Volumetric Modulated Arc Therapy) technique were prepared. Each plan used two VMAT arcs with a photon energy of 6 X MV. All plans were calculated using a Monte Carlo calculation algorithm with an uncertainty of 0.5 %. Irradiation time was estimated by the treatment planning system. Dose proscribed was 25 Gy in one fraction like in HDR-BT. Treatment planning for CK SBRT and LINAC SBRT was optimised for PTV while maintaining tolerance doses for organs at risk. The dose constraints for OARs are given in Table 1.

Definition of selected endpoints

The doses delivered to the PTVs D98%, D90%, D50% and V30Gy, V25Gy, V23.75Gy were calculated and reported for evaluation. Also, comparisons of selected conformity indexes were prepared, with their definitions presented in Table 2 [21,22]. The V10Gy liver volume was also selected for evaluation as a parameter previously connected with radiation-induced liver disease (RILD) [23,24]. The uninvolved liver was defined as liver volume minus PTVbt for each radiotherapy modality.

Statistical analysis

The obtained results were included in the statistical analysis. The values of the analysed measurable parameters were presented using the median and standard deviation values. For measurable features, the normality of the distribution of the analysed parameters was assessed using the Shapiro-Wilk W test. The Wilcoxon pairwise order test was used to compare the analysed treatment methods. The significance level of $p < 0.05$ was adopted, indicating the existence of statistically significant differences or relationships. The database and statistical tests were carried out using STATISTICA version 13.0 computer software (StatSoft, Poland).

Results

Thirty patients (11 females and 19 males with a median age of 70 years) with a median size of the liver metastasis of 3.09 ± 0.62 cc and a median of an uninvolved liver volume of 1441.08 ± 369.27 cc were included. The median number of HDR-BT applicators used was 1 (1–3). Single dose of 25 Gy was used in all cases. The mean PTVbt was 9.08 ± 5.70 cc (median 7.02 cc). The mean PTV for SBRTck and SBRTe was 25.05 ± 11.27 cc (median 22.07 cc). The treatment delivery time was comparable between HDR-BT and SBRTe (median of 6.7 ± 2.61 min vs. 5.8 ± 0.65 min), while the median SBRTck treatment time was 59 ± 4.36 min. Fig. 1 shows an example of dose distribution between selected radiotherapy modalities in a patient with metastasis localized in the 5/6 liver segment.

PTVs dose coverage

HDR-BT plans resulted in better dose coverage with the prescribed

Table 2
Conformity indexes used for comparison.

R100% (Prescription dose spillage)	**Vol (100 %)PTV V100%**
R50% (Modified Gradient Index)	**Vol (50 %)PTV V100%**
PCI (Paddick Index)	**(PTV V100% or CTV V100%)2(V PTV or V CTV) *Vol (100 %)**
HI (Homogenity Index)	**D2%-D98%D50%**

CTV V100% – volume of the target covered by prescription isodose, D2% – the minimal dose to the 2% highest irradiated target volume, D50% – the minimal dose to the 50% highest irradiated target volume, D98% – the minimal dose to the 98% highest irradiated target volume, PTV V100% – volume of the target covered by prescription isodose, Vol (50%): the volume of the patient covered by half of the prescription isodose, Vol (100%): the volume of the patient covered by prescription isodose, V PTV-PTV volume, V CTV-CTV volume.

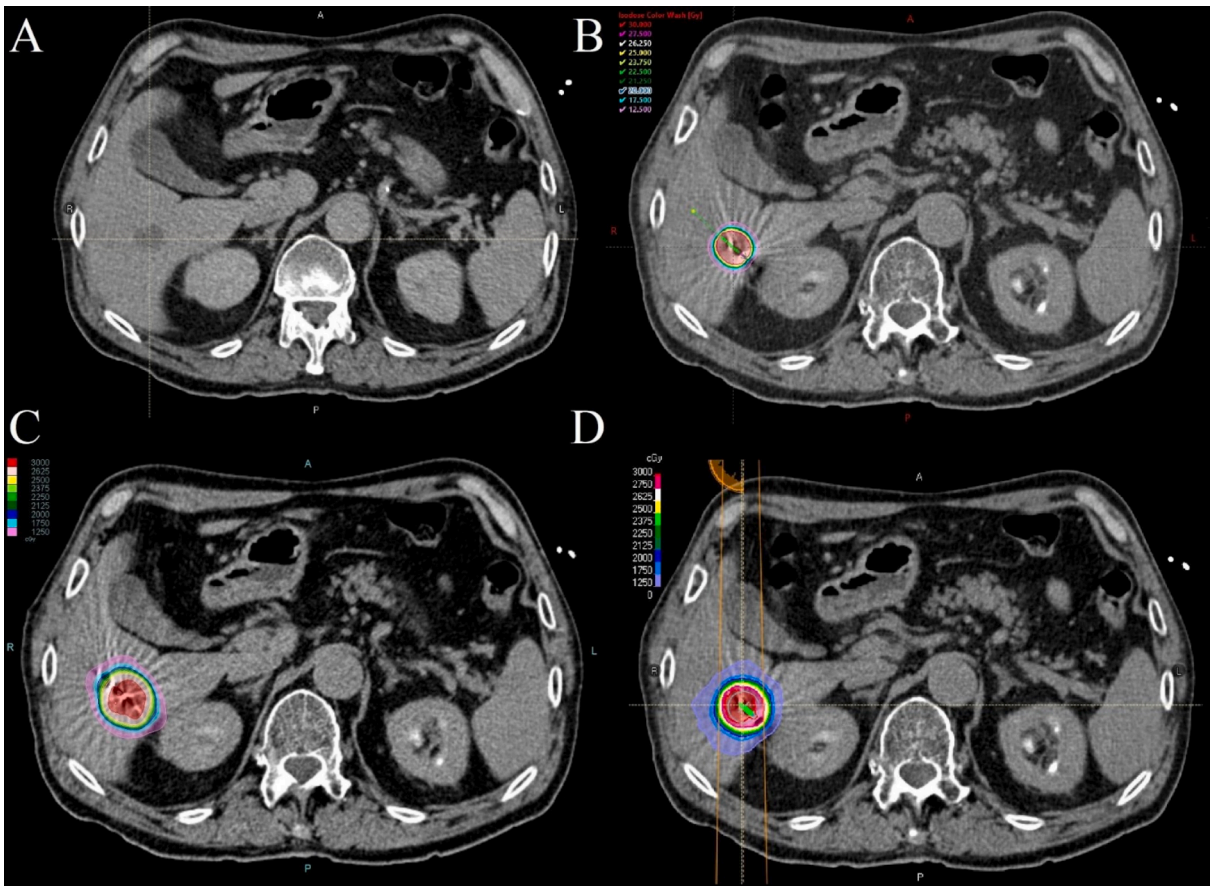

Fig. 1. Exemplary view of one of selected patients treated with brachytherapy/ interventional radiotherapy and dose distribution profiles for selected MDT modalities: diagnostic image before treatment (A), HDR-BT (B), SBRTck (C) and SBRTe (D).

25 Gy dose, than both SBRT modalities. Dmean, D50%, and D90% values were significantly higher for HDR-BT plans than for SBRTe ($p < 0.001$ for all values) and SBRTck ($p < 0.001$ for all values). Between both SBRT modalities, SBRTck plans resulted in better dose coverage, as revealed in Dmean, D50%, and D90% values compared to SBRTe ($p = 0.01$, $p < 0.001$ and $p = 0.02$, respectively). There were opposite results presented in the D98% value. SBRTe approached better than HDR-BT, but there was only a trend in favour of SBRTck ($p = 0.03$ and $p = 0.07$, respectively). HDR-BT plans resulted in higher V30Gy compared to SBRTe and SBRTck ($p < 0.001$ for both) and SBRTe performed better than SBRTck ($p < 0.001$, Fig. 2). V100 (V25Gy) was comparable between techniques. A detailed overview of dose coverage is given in Supplementary Material (Table S1).

Conformity indices comparison

The best median PCI and R100% was achieved with SBRTe plans. It was significantly better than HDR-BT ($p < 0.001$) and SBRTck ($p < 0.001$). SBRTck also achieved better median PCI values than HDR-BT ($p < 0.001$). HI was also better for SBRTe and SBRTck than in HDR-BT plans ($p < 0.001$ for both), with the best results obtained for SBRTck ($p < 0.01$). Similar trends were seen regarding the R50% value, except for SBRTe vs. SBRTck, where no significant differences were found ($p = 0.81$) (Table 3).

Dosimetric dose distribution in OARs

Uninvolved liver volume (V5Gy, V9.1 Gy, V10 Gy, D66%)

The lowest median doses delivered to uninvolved liver volume, according to the V9.1 Gy value, were achieved with HDR-BT. It differed significantly between HDR-BT vs. SBRTe ($p < 0.001$) and between HDR-BT vs. SBRTck ($p < 0.001$), while the difference between SBRT modalities was insignificant ($p = 0.11$). The analysis of the V10Gy value showed similar results. Significantly lower doses, including D66%, were reached by SBRTe in comparison to HDR-BT and SBRTck ($p < 0.001$ for both) (Table 4). The evaluation of the parameters: V5Gy(%) and V5Gy (cc) showed that higher values were obtained for the SBRTe and SBRTck methods compared to HDR-BT, which confirms that HDR-BT is technique which delivers the lowest dose to uninvolved liver volume.

Dose distribution in other OARs

The analysis of doses delivered to other organs revealed significant differences between radiotherapy modalities for almost all organs, except for the bowel and biliary tract. Fig. 3 depicts major variations in dose distribution among selected OARs. The detailed analysis of doses delivered to all selected OARs is included in Table S2 in Supplementary Materials.

Ribs

According to Dmax and D1 cc values, the lowest median doses were achieved by HDR-BT plans compared to SBRTe and SBRTck modalities ($p < 0.001$ for all). Between both SBRT modalities, only the median D1cc value was better for SBRTck ($p = 0.01$).

Duodenum

Regarding Dmax value SBRTck achieved lower median doses than HDR-BT ($p = 0.02$). The same trend was seen in regard to D1cc, D5cc, and D10cc values in favour of SBRTe and SBRTck plans. Median doses within Dmax, D1cc, D5cc, D10cc values did not differ between SBRT modalities.

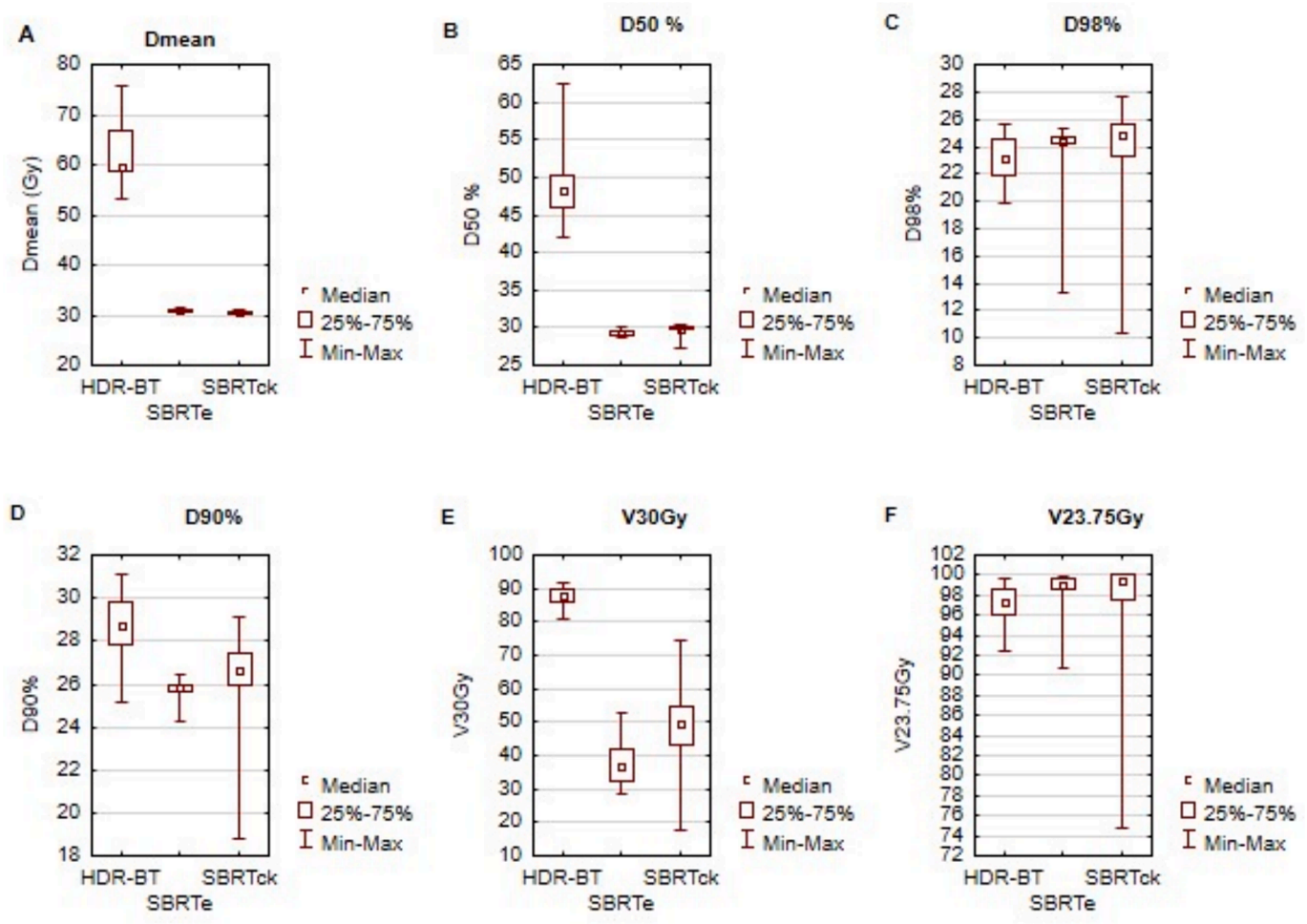

Fig. 2. The comparison of doses delivered to PTVs between HDR-BT, SBRTe and SBRTck.

Stomach

The lowest median doses according to Dmax, D1cc and D10cc values were presented by HDR-BT plans. The differences were seen between HDR-BT vs. SBRTe and SBRTck. SBRTck plans were also better than SBRTe plans in all selected dosimetric values.

Bowel, biliary tract and gallbladder

There were no differences according to Dmax for bowel, and biliary tract and D5cc for bowel values between selected radiotherapy modalities except better Dmax value for gallbladder in favour for SBRTe plans vs. HDR-BT plans ($p < 0.001$). (See Fig. 4).

Esophagus

HDR-BT plans achieved lower D1cc values in comparison to both SBRT modalities. Dmax dose distribution also favoured HDR-BT compared to SBRTck and SBRTe ($p < 0.001$ for both). SBRTck plans also showed better Dmax and D1cc values compared to SBRTe plans ($p < 0.01$ and $p = 0.04$, respectively).

Right kidney (Kidney R)

HDR-BT plans achieved higher D100cc and Dmean values in comparison to both SBRTe and SBRTck while there was no difference according to D1cc value between the three modalities. Comparison between both SBRT modalities favoured SBRTe according to Dmean and D100cc ($p = 0.004$ and $p < 0.01$, respectively).

Heart

The lowest median Dmax value was achieved with HDR-BT plans. HDR-BT plans approached better compared to SBRTck plans ($p = 0.02$). There were no differences between both SBRT modalities.

Great vessels

The lowest median doses according to D1cc value was presented by HDR-BT plans. The differences of strong significance were seen between HDR-BT vs. SBRTe and HDR-BT vs. SBRTck modalities ($p < 0.001$ both). SBRTck plans showed lower D1cc doses than SBRTe plans ($p < 0.001$).

Skin

HDR-BT plans achieved lower D10cc and Dmax doses in comparison to both SBRT modalities ($p < 0.001$ for all). SBRTck plans presented lower doses according to D10cc and Dmax values compared to SBRTe plans ($p = 0.001$ and $p < 0.001$, respectively).

Spinal cord

The lowest median doses according to Dmax, D0.35 cc, D1cc and D1.2 cc values were presented by HDR-BT plans vs. SBRT modalities ($p < 0.001$ for all). SBRTck performed better than SBRTe in all selected values.

Discussion

Radiation-based local ablative therapies for liver lesions are very valuable treatment options for unresectable lesions [1–6]. HDR-BT for liver malignancies is emerging as a viable alternative to SBRT. However, the technique is only accessible in specialized centres with a proficient brachytherapy service. The decision on which of those techniques could

Table 3
The comparison of selected indices between HDR-BT, SBRTe, and SBRTck modalities.

Indices	HDR-BT Median ± SD	SBRTe Median ± SD	SBRTck Median ± SD	Analysis
PCI	0.55 ± 0.11	0.93 ± 0.03	0.81 ± 0.09	HDR-BT vs. SBRTe* p < 0.001 HDR-BT vs. SBRTck* p < 0.001 SBRTe* vs. SBRTck p < 0.001
HI	3.13 ± 0.77	0.27 ± 0.10	0.22 ± 0.13	HDR-BT vs. SBRTe* p < 0,001 HDR-BT vs. SBRTck* p < 0.001 SBRTe vs. SBRTck* p < 0.01
R50%	4.50 ± 1.15	3.63 ± 0.38	3.57 ± 0.58	HDR-BT vs. SBRTe* p < 0.001 HDR-BT vs. SBRTck* p < 0.001 SBRTe vs. SBRTck p = 0.81
R100%	1.63 ± 0.36	1.04 ± 0.02	1.19 ± 0.12	HDR-BT vs. SBRTe*p < 0.001 HDR-BT vs. SBRTck* p < 0.001 SBRTe* vs. SBRTck p < 0.001

* Favours selected radiotherapy modality.

be chosen is usually based on patient-related factors, the size, location and number of the lesion, and the patient's preferences. The evaluation of dosimetry parameters comparing several treatment techniques is not routinely performed due to various reasons.

This study evaluates interstitial HDR-BT and SBRT in terms of the dose exposure of organs at risk (OAR) and target dose coverage. A plan comparison was conducted to virtual SBRT plans using the original HDR-BT planning CT. So far, only a few reports have compared SBRT and HDR-BT, with fewer studies using virtual treatment planning [2,9,11,25]. Pennington et al. compared the dosimetry differences of BT and SBRT using data sets of 10 patients with liver lesions. Patients who were initially planned for SBRT, had BT plans virtually replanned using five fractions of 12 Gy to the SBRT PTV. Their study indicated that BT could result in a higher target dose, and the mean volume receiving 150 % of the prescribed dose was significantly higher for virtual BT plans. They reported that the minimum dose to the PTV, which was significantly lower for BT, resulted in lower target coverage, although similar doses to nearby OARs were achieved in both techniques [25]. In our study, we observed comparable results, with better coverage (except for D98%) in HDR-BT plans in contrast to SBRT modalities. In our study, the lower values of the "near-minimum" D98% parameter for PTV in HDR-BT may be the result of the steep dose gradient observed in interstitial implants, which is an intrinsic and inevitable feature of the brachytherapy technique. This may raise concerns about whether the low minimum dose affects local control. Rick et al. in their study on CT-guided brachytherapy in colorectal liver metastases correlated local control with the minimum dose delivered to the target, indicating the importance of the target coverage with the prescribed dose to avoid the cold spots (the volume that receives the dose below the prescribed dose) in the target [27]. Single fraction dose escalation study in liver tumours, with 35–40 Gy in single fraction, shows promising results according to excellent local control and tolerance [28].

In our study, the mean PTV dose values achieved with HDR-BT were

Table 4
The comparison of uninvolved liver volume exposure between HDR-BT, SBRTe and SBRTck modalities.

OARs		HDR-BT	SBRTe	SBRTck	p value
Organ	DVH value	median ± SD	median ± SD	median ± SD	
Uninvolved Liver	V9.1 Gy	38.73 ± 24.21 cc	92.07 ± 60.07 cc	84.36 ± 59.95 cc	HDR-BT* vs. SBRTe p < 0.001 HDR-BT* vs. SBRTck p < 0.001 SBRTe vs. SBRTck p = 0.11
	V10Gy	33.49 ± 20.74 cc	80.84 ± 47.24 cc	75.25 ± 51.79 cc	HDR-BT* vs. SBRTe p < 0.001 HDR-BT* vs. SBRTck p < 0.001 SBRTe vs. SBRTck p = 0.34
	D66%	0.57 ± 0.30 Gy	0.26 ± 0.26 Gy	0.61 ± 0.48 Gy	HDR-BT vs. SBRTe*, p < 0.001 HDR-BT vs. SBRTck p = 0.28 SBRTe * vs. SBRTck p < 0.001
	V5Gy	6.49 ± 3.74 %	13.69 ± 7.55 %	13.50 ± 8,77 %	HDR-BT vs. SBRTe*, p < 0.001 HDR-BT vs. SBRTck* p < 0.001 SBRTe vs. SBRTck p = 0.84
	V5Gy	93.41 ± 54.67 cc	186.69 ± 132.68 cc	175.67 ± 139.97 cc	HDR-BT vs. SBRTe*, p < 0.001 HDR-BT vs. SBRTck* p < 0.001 SBRTe vs. SBRTck p = 0.89
	D33%	1.15 ± 0.62 Gy	1.42 ± 1.46 Gy	1.94 ± 1.38 Gy	HDR-BT vs. SBRTe, p = 0.10 HDR-BT vs. SBRTck* p < 0.001* SBRTe vs. SBRTck* p = 0.001

* Favours selected radiotherapy modality.

significantly higher than with SBRT techniques and tumour volume received at least twice the dose from external beam techniques. Several authors investigated the potential of CK, proton therapy and SBRT to mimic the dose distributions of HDR brachytherapy of prostate cancer [29,30]. In both studies a target volume covered with 200 % of the prescribed dose was not larger than 11 % (median for analysed group). In HDR-BT, maximum doses are much higher, especially close to the sources, allowing to escalate the dose within the target higher than in other techniques.

Wust et al. showed a result of a dosimetric study comparing HDR-BT with SBRT performed on CK, VMAT and tomotherapy used 20 Gy in a single fraction. Dmean and other therapeutic ratios as well as doses to

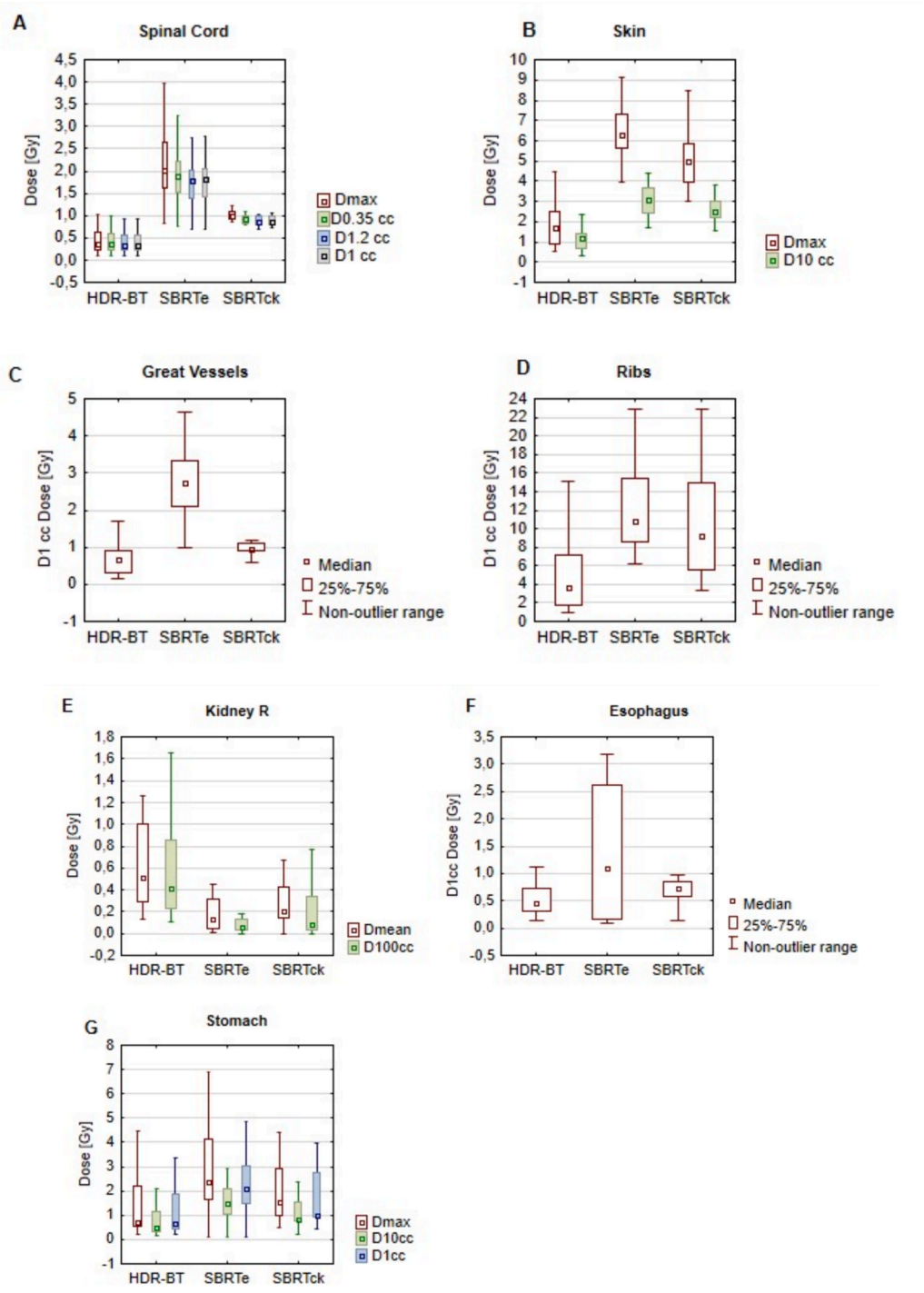

Fig. 3. The comparison of doses delivered to OARs between HDR-BT, SBRTe and SBRTck (A – spinal cord, B – skin, C – great vessels, D – ribs, E – right kidney, F – esophagus, G – stomach).

OARs were better for HDR-BT, especially for tumours smaller than 3 cm [26]. Similar to our analysis, Hass et al. reported the comparison of dosimetry parameters of 85 patients who were initially treated with BT (total dose in the range of 15–20 Gy) and had virtually created SBRT plans. As in our study, additional margins were added to the target for SBRT, which resulted in a much larger PTV volume of SBRT target compared to HDR-BT. Their results indicated that HDR-BT can achieve the targeted prescription dose of 15 Gy/20 Gy better than SBRT without violating OARs constraints. Furthermore, it should be noted that the liver exposure was significantly lower with HDR-BT, even though this could be anticipated due to the size of the PTV in both techniques [9]. These observations are in accordance with our analysis, and the lowest median doses delivered to uninvolved liver volume, according to the V5Gy and V9.1 Gy value, were achieved with HDR-BT, while the difference between SBRT modalities was insignificant. These results provide a good understanding of the theoretical advantages of the respective radiation technique, but a single fraction SBRT of liver malignancies with a prescribed dose of 15 Gy is not a clinically validated treatment regimen as well as 25 Gy in one fraction. Walter et al. in his HDR vs. SBRT comparison study found, similarly to us, that the volume of uninvolved liver exposure was smaller in HDR BT than in SBRT, suggesting an advantage of HDR BT for normal liver tissue sparing [2].

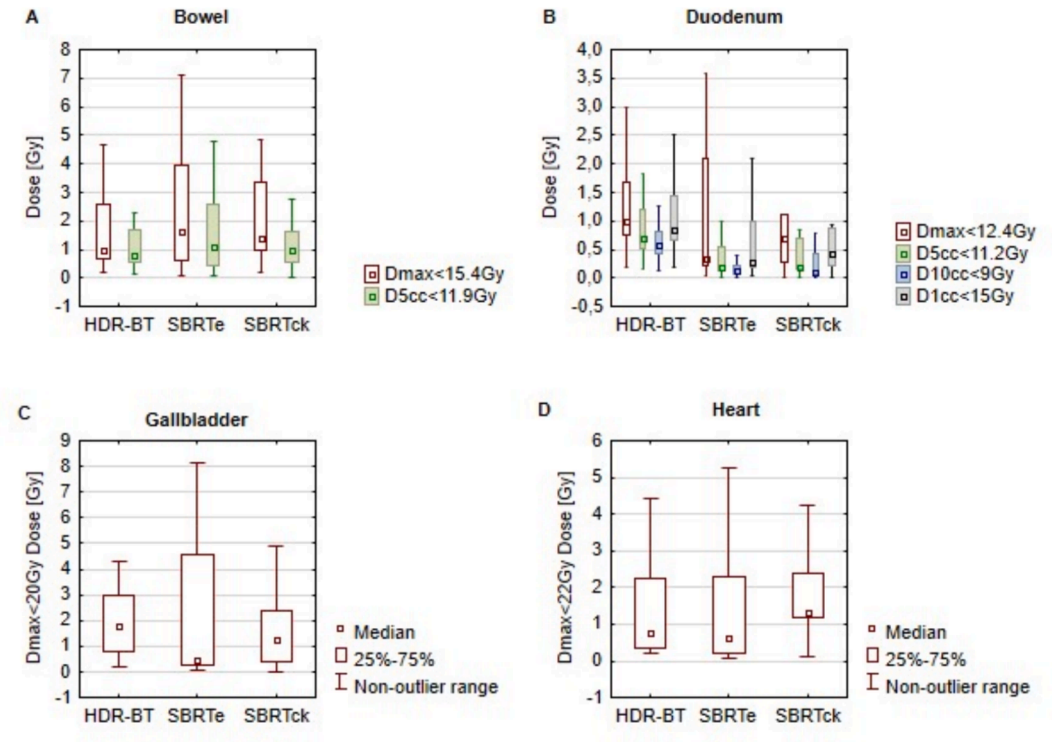

Fig. 4. The comparison of doses delivered to OARs between HDR-BT, SBRTe and SBRTck (A – bowel, B – duodenum, C – gallbladder, D – heart).

Regarding the fact that liver function sparing is important in the case of patients with primary or secondary cancers, the parameter of uninvolved liver tissue needs to be considered during the plan analysis. Walter el al., as well as Wust et al. evaluated the dose delivered in the uninvolved liver regarding the size of the lesions showing that the greatest advantage of HDR-BT is observed in the case of larger lesions [2,26].

The calculated treatment delivery time in our analysis was comparable between HDR-BT and SBRTe, while the median SBRTck treatment time was significantly longer. Long treatment times can increase the uncertainty of dose delivery, even when highly specialized methods are used to track and verify patient positioning. HDR-BT allows relatively rapid dose delivery, but patient eligibility criteria must consider the invasiveness of the method and location of the lesions. It is difficult to compare treatment times for different techniques. In brachytherapy, the treatment time depends on the activity of the source. As the activity decreases, the treatment time increases. This may have an effect on the statistical significance of differences between treatment times for different techniques. In our study, we emphasised that the treatment time was calculated at a nominal activity of 10 Ci. This information allows to estimate the relative time needed to deliver the dose for other activities of the source. We also have to consider the need for fiducial marker's implantation during SBRTck preparation, which makes it also, in general, an invasive procedure, but not all the patients had to undergo this to be able to receive SBRT for liver lesions. However, the placement of brachytherapy catheters requires some form of anesthesia, which, compared to small fiducial implantation not requiring the sedation of the patient, is a much more invasive procedure. What is more, patients suitable for HDR-BT must meet the criteria: good performance status (WHO < 3), tumour diameter below 10 cm, number of metastases ≤ 5, technical possibilities of application of catheters (lack of large vessels in close proximity to the lesions), creatine level below 2 mg/dl, haemoglobin > 8 mg/dl, white blood cells $> 2000/mm^3$, neutrophils $> 1500/mm^3$, platelets $> 50000/mm^3$, INR < 1.5, liver enzymes < 2.5 upper normal limit. Patients who don't meet those criteria, as well as those with target in close proximity of large vessels or with other OARs close to the target, which prevents the achievement of the planned dose without compromising of doses delivered to OARs, and those with any form of inflammation inside the abdominal cavity, were excluded and not offered HDR-BT. Some of those HDR-BT contraindications (like blood tests, patients performance status) are also contraindications for SBRT, however those with OARs close to the target and larger number of lesions could be possible candidates for SBRT.

All irradiation techniques, evaluated in our study, have both advantages and disadvantages. In the case of HDR-BT, in some cases, location of lesions or patient anatomy might limit optimal applicators positioning. In this respect, external beam techniques, which include CK and linear accelerators, will achieve noticeably better results in tumour coverage (D98) and adaptation of the reference isodose to the target shape, i.e., conformity and PCI.

The current study has several limitations due to its retrospective nature. Firstly, this patient cohort was already selected as suitable patients for HDR-brachytherapy. Specifically, the virtual calculation of SBRT plans was performed without considering additional larger, possible movements of liver which might have possibly been translated into much larger PTVs for SBRT planning. What is more, prescribed dose of 25 Gy in one fraction is not routinely used in practice for liver metastases SBRT, with the favour of fractionated regimens. Additionally, the histopathology of liver metastases was not a selection criterion for the purpose of this study. This might be regarded as a limitation, since some of the surgical studies with patients with colorectal liver metastases showed the benefit of more extensive margins. The number of cases included in the analysis was low, but comparable to the previously published studies. None of the so far published similar dosimetric analysis, compared three selected by our group, radiotherapy modalities in patients with liver metastases.

Conclusion

HDR-BT resulted in more favourable dose distribution within PTVs and lower doses in organs at risk, which suggests that this treatment modality may be regarded as an alternative to other local ablative

therapies in carefully selected patients' with liver malignancies. Future studies should further address the issue of comparing treatment modalities in different liver locations and clinical scenarios.

CRediT authorship contribution statement

Mateusz Bilski: Conceptualization, Data curation, Investigation, Methodology, Project administration, Resources, Writing – original draft, Writing – review & editing. **Katarzyna Korab:** Data curation, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Małgorzata Stąpór-Fudzińska:** Data curation, Investigation, Writing – original draft, Writing – review & editing. **Julia Ponikowska:** Data curation, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Agnieszka Brzozowska:** Formal analysis, Software, Visualization. **Łukasz Sroka:** Data curation, Resources, Software, Visualization, Writing – original draft, Writing – review & editing. **Ewa Wojtyna:** Data curation, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Sylwia Sroka:** Data curation, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Marta Szlag:** Data curation, Investigation, Methodology, Writing – review & editing. **Paweł Cisek:** Supervision. **Aleksandra Napieralska:** Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing.

Declaration of competing interest

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.ctro.2024.100815.

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