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Impact of tumor anatomic characteristics on patient radiation dose during transarterial chemoembolization

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ABSTRACT

Objective: The aim of the study was to determine the association between anatomic tumor characteristics and the radiation dose in patients with hepatocellular carcinoma undergoing transarterial chemoembolization (TACE).

Materials and Methods: A retrospective study was performed over a 42 months period. A total of 51 TACE procedures were included in the study. Information collected included: Gender, BMI, height, weight, cumulative dose area product (KAP), cumulative reference air kerma (RAK), maximum tumor diameter, multinodular tumors, and embolization material. Parametric univariate and simple linear regression analysis were used to determine associations between quantitative variables.

Results: A total of 51 procedures in 37 patients, 19 women (51%) and 18 men (49%), with a mean age of 56 years (±17.3 years) and a mean BMI of 24 kg/m^2 were included in the study. Overall, patient radiation dose was as follows: Mean KAP of 542.2 Gy* cm^2 (±307 Gy* cm^2) with a mean RAK of 2930.2 mGy (±1776.5 mGy). Higher patient radiation doses were observed in men (581.6 ± 262.9 Gy* cm^2 vs. 497.8 ± 350.5 Gy* cm^2) ($P = 0.06$) and in patients with higher BMIs (KAP: $r = 0.37$ [$P = 0.01$]; RAK: $r = 0.4$ [$P = 0.01$]). Patients with multinodular disease were found with lower radiation dose according to RAK (1710.7 ± 1118.6 mGy vs. 3227.7 ± 1789.1 mGy, $P = 0.03$). Furthermore, logistic regression analysis demonstrated that patients with multinodular disease received 10% lower dose, according to RAK, when compared to patients with single tumors (odds ratio 1.001, 95% confidence interval [CI], 1–1.002) ($P = 0.02$).

Conclusion: TACE is an effective method to treat patients with HCC that may be performed within acceptable radiation dose limits. Anatomic tumor characteristics were found to be associated with patient radiation dose. Interestingly, multi-tumor disease was found to cause a radiation dose reduction of 10%.

Keywords: Transarterial chemoembolization, Hepatocellular carcinoma, Anatomic tumor characteristics, Radiation dose

INTRODUCTION

Fluoroscopically guided interventions are more often indicated for diagnosis and treatment of patients unsuitable for surgical therapy because of high risk.[1-3] Minimally invasive interventions have increased in frequency and in complexity, therefore, higher radiation exposure is required to complete the treatment.[4] Often, higher radiation doses are obtained despite the continuous development of fluoroscopic technology. At present, case type remains a major factor in determining radiation dose.[5]

The use of fluoroscopically guided interventions for oncologic indications has increased over the past several decades. The treatment of liver tumors classified as "unresectable" represents one of the main indications for fluoroscopically guided interventions in oncology.[6]

Transarterial chemoembolization (TACE) is an effective, minimal invasive procedure aimed to treat patients with unresectable hepatocellular carcinoma (HCC) under fluoroscopic guidance.[7,8] Often, patients undergoing TACE need to be treated with consecutive embolization sessions, which increase patient radiation exposure.[7,8]

Using fluoroscopy guidance during TACE, the selective catheterization of the hepatic arteries is performed to assess segmental hepatic and tumor vascularity before the administration of the chemotherapeutic agent.[9-11] Often, tumor anatomy is complex, which requires interventionists to use prolonged fluoroscopy times and numerous images.[12] In patients with single or low number of tumors, super selective tumor vasculature catheterization is indicated with optimal imaging quality.[13] The use of multiple and high quality images on complex cases, therefore, may increase radiation doses to patients and interventionists.

The previous studies have reported radiation exposure of patients and interventionists during TACE. All the studies have demonstrated that TACE may be performed under safe radiation thresholds. However, radiation exposure remains as an important topic of investigation among interventionists. Recently, authors have aimed to find parameters that decrease radiation dose. Most of the prior studies are focused on the development of X-ray equipment with advanced technical parameters that reduce radiation without affecting image quality, such as the use new imaging platforms. The impact of anatomic parameters and procedure complexity, however, has not been analyzed and reported.

To the best of our knowledge, no studies have assessed the association between TACE complexity by tumor anatomic characteristics and patient radiation dose. Therefore, the aim of this study is to determine the association between TACE complexity by tumor anatomic characteristics and radiation dose among patients with hepatocellular carcinoma undergoing TACE.

MATERIALS AND METHODS

Study population

Patients older than 18 years with HCC not eligible for surgical therapy that underwent TACE were included in the study. Patients unsuitable for surgical therapy included lesions beyond the Milan criteria, including multifocal tumors (more than 3 nodules >3 cm), patients with severe portal hypertension, single tumor >5 cm and/or patients unfit for open surgery secondary to comorbidities.

Diagnosis of HCC was based on imaging criteria using baseline multiphase hepatic CT scans and MRIs. In patients with non-classical imaging findings of HCC, histologic confirmation was required. All the patients were retrospectively enrolled in the study. Secondary TACE sessions were performed by the same interventional staff using the same equipment and interventional techniques.

Patients were excluded from the study if at least one-inclusion criterion was not met. Similarly, patients previously treated with TACE and/or treated outside our institution were excluded from the study.

TACE

Percutaneous femoral access was used in all cases. Selective catheterization of tumor vascularity was performed under fluoroscopic guidance. The standardized dose of doxorubicin was 50 mg for all chemoembolizations in two different combinations, as follows: Doxorubicin+ Lipiodol (Lipiodol® Ultra Fluid, Guerbet Group, Villepinte, France) or 300–500 μm polyvinyl alcohol (PVA) particles (Cook Medical, Bloomingdale, USA) combined with doxorubicin according to interventionist criteria. The selection of embolization material was based on tumor size, baseline liver function, and product availability. For larger tumors (usually >5 cm) with preserved functionality (Child-Pugh A or low MELD score), and at low risk for post-treatment liver dysfunction secondary to embolization toxicity, Lipiodol + doxorubicin was selected. In patients, with Child-Pugh B and/or high baseline MELD score, the use of doxorubicin + PVA particles was preferred. Similarly, patients with tumors <5 cm were more often treated with doxorubicin + PVA particles. As part of TACE protocols, aortic, selective celiac, and hepatic angiographies were performed.

All the procedures were performed by the same interventionist at the same medical center. The interventionist was a certified interventional radiologist with 15 years of experience performing TACE. Similarly, our institution is a third-level medical center with a national referral network for oncology. The routine use of TACE for HCC has been performed at our institution since 2004.

Fluoroscopy equipment and radiation dose

All TACE procedures were performed using the Siemens AXIOM-Artis dTA equipment (Siemens Healthcare, Erlangen, Germany). Standard equipment positioning was maintained during the main extent of TACE with the X-ray source located underneath the patient and the image receptor above. Therefore, posterior to anterior X-ray direction was mainly used during TACE (0°). The C-arm was mobile around a free-floating theater table and capable to obtain mid-sagittal rotations (90°) for true lateral angulations. Angulations between 0° and 90° are referred as "anterior-oblique (AO)." The monitor screens were located on the left-hand side of the patient, with interventional staff standing on the right side [Figure 1].

The fluoroscopy equipment was operated using low dose mode and was controlled by a radiology technician. Pulse fluoroscopy mode was used for all procedures with a pulse rate of 10 pulses per second. Digital subtraction angiography (DSA) acquisitions were obtained at a pulse rate of 2 pulses per second. The patient to image intensifier was minimized as possible. Field size and magnification were maintained according to "As Low As Reasonably Achievable" principles with collimation application when possible.[14]

Patient radiation dose was collected from fluoroscopy equipment, including Kerma-area Product (KAP, Gy*cm^2) and reference air kerma (RAK, mGy). KAP is defined, as a measure of the total X-ray energy output of the X-ray tube and therefore, it approximates the total X-ray energy absorbed by the patient. The RAK is the kinetic energy released in the medium at interventional reference point, which is located 15 cm along the beam axis toward the focal spot from isocenter [Figure 2]. The RAK provides an estimate of the air kerma at the entry point of the patient's skin and therefore, it approximates patient's skin dose.[2,15,16]

Study design and outcomes

After institutional board review (IRB) approval (IRB approval number: 09-CEI-019-20160729), a retrospective, single arm, and single center study was performed over a 42 months period. All the procedures included in this study were performed between January 2014 and July 2017. A waiver to the informed consent form was requested and approved by the IRB because of the retrospective nature of the study. Patient radiation dose, expressed as KAP and RAK, was the primary endpoint of the study. We hypothesize that procedure complexity, defined by anatomic characteristics, is significantly associated with increased patient radiation dose.

Statistical analysis

Shapiro–Wilk and Kolmogorov–Smirnov tests demonstrated non-normal distribution of KAP and RAK. Therefore, logarithmic transformation was performed to obtain normal distribution of radiation data. Anatomic characteristics, however, failed to demonstrate normal distribution after logarithmic transformation. Therefore, non-parametric Spearman test was used to assess correlation between anatomic characteristics and radiation dose. Quantitative variables were reported as means and standard deviation. Categorical variables were reported as percentages. Independent group, two-sample student *t*-test was used to compare continuous variables. Independent predictors found to be significantly associated with radiation dose on univariate analysis were included in a simple and multiple regression analysis. Data analysis was performed using SAS 9.4 software (SAS Institute, Cary, NC). All statistical tests were two-sided, and differences were considered significant at $P < 0.05$.

RESULTS

A total of 51 TACE procedures were performed in 37 patients, 19 women (51%) and 18 men (49%), over a 42 months period. The mean age of the cohort was 56.5 years (±17.3 years) with a mean BMI of 24 kg/m^2. Mean tumor diameter at the time of TACE was 6.4 cm (±3.4 cm). In ten patients (27%), multinodular disease was observed

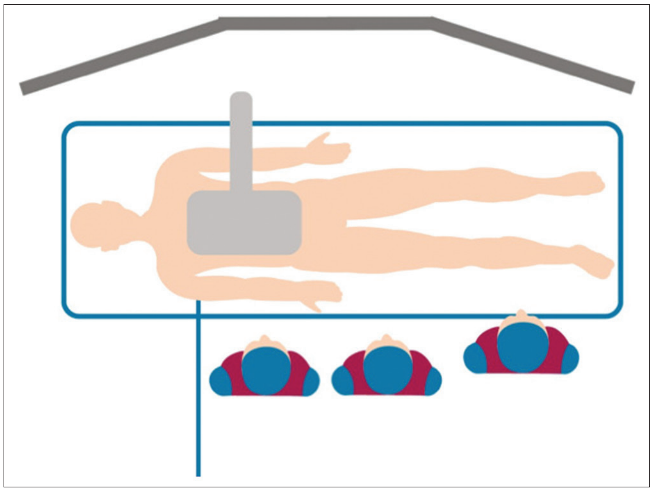

Figure 1: Diagram illustrates patient, equipment and interventionist positioning during TACE.

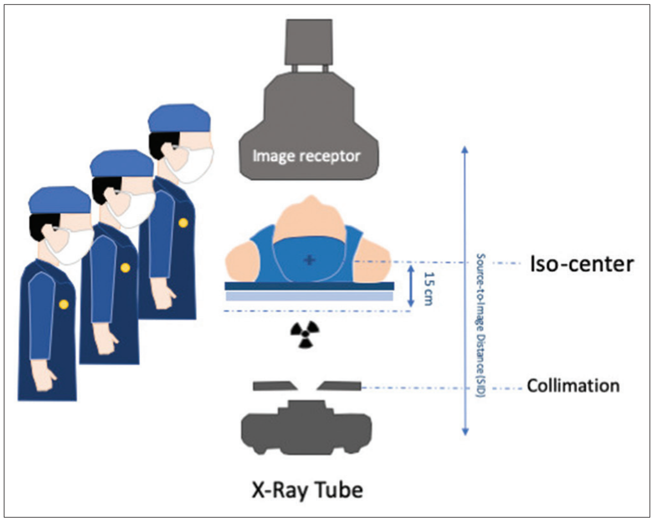

Figure 2: Reference Air kerma. Source-to-image distance, international reference point and interventionist positioning.

diagnosed. A total of eight patients (22%) required more than 1 TACE at a mean time of 6 months (±2 months). In 30 (73%) procedures, tumor embolization was performed using Lipidol + doxorubicin. The mean fluoroscopy time was 26.9 min (±13.8) with a mean number of DSA runs of 13 (±8.1). Overall, the patient radiation dose was as follows: Mean KAP of 542.2 Gy* cm^2 (±307 Gy* cm^2) with a mean RAK of 2930.2 mGy (±1776.5 mGy) [Table 1].

In our cohort, male patients received higher radiation doses according KAP compared to women (581.6 ± 262.9 Gy* cm^2 vs. 497.8 ± 350.5 Gy* cm^2) (P = 0.06) [Figure 3]. Similarly, patients with higher BMI demonstrated higher radiation doses according to KAP and RAK (r = 0.37 [P = 0.01] and r = 0.4 [P = 0.01], respectively) [Figures 4a and b]. As expected, the number of digital DSA series was correlated to higher radiation dose according to KAP and RAK (r = 0.6 [$P < 0.01$] and r = 0.76 [$P < 0.01$], respectively).

Table 1: Baseline characteristics, intraoperative technical parameters, and radiation dose.

Variables	No. of patients (%)
Gender	
Male	18 (49)
Female	19 (51)
Mean (±)	
Age	56 (17.3) years
BMI	24 (5.03) kg/m^2
Height	
Male	165 (0.05) cm
Female	153 (0.04) cm
	P=0.01
Weight	
Male	66(16) kg
Female	60 (10) kg
	P=0.1
Field of view (FOV)	Median 42 cm
	Interquartile range (IQR), 32–48
Tube voltage	Median 84 kVp
	IQR, 82–86
KAP	542.2 (±307) Gy* cm^2
RAK	2930.2 (±1776.5) mGy

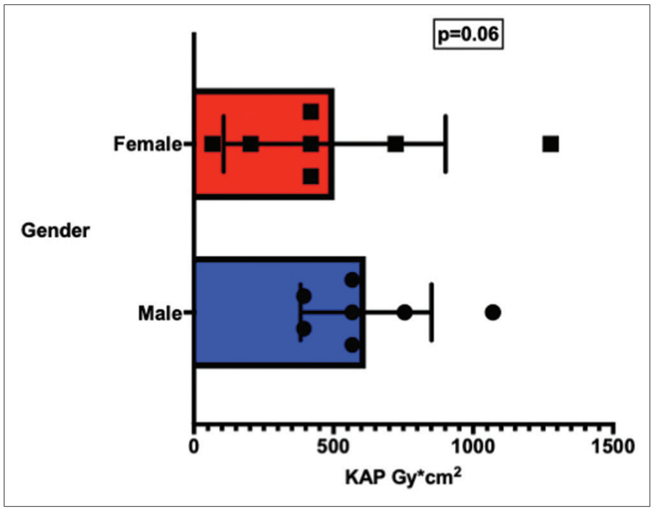

Figure 3: Patient radiation dose according to KAP by gender.

Interestingly, patients with multinodular disease were found to have a lower radiation dose than patients with single lesions, according to RAK (1710.7 ± 1118.6 mGy vs. 3227.7 ± 1789.1 mGy, P = 0.03) [Figure 5a]. In fact, the number tumors demonstrated an inverse correlation with radiation dose according to RAK (r = −4, P = 0.03) [Figure 5b]. Similarly, a smaller number of DSA runs was required for patients with multinodular disease (11 [±3] vs. 13 [±8], respectively, [P = 0.05]). In patients with multiple lesions, staged treatment was performed in 80% of the cases. When other anatomic tumor parameters were added to the analysis, only tumors with a larger diameter demonstrated a weak correlation with patient radiation dose, according to RAK (r = 0.29, P = 0.09). Tumor size, however, demonstrated a negative correlation with fluoroscopy time (r = −0.34 [$P < 0.01$). Remarkably, the use of different embolization materials failed to demonstrate association with radiation dose, according to KAP and RAK (P = 0.1).

For multivariate linear regression analysis, all the parameters with significance on univariate analysis were included in the study. None of these events reached statistical significance. Logistic regression analysis, however, demonstrated that patients with multinodular disease received 10% lower dose, according to RAK, when compared to patients with single tumors (odds ratio=1.001; 95% confidence interval [CI], 1–1.002) (P = 0.02).

DISCUSSION

TACE is an effective and safe procedure that may be performed within secure radiation dose limits in patients with HCC unsuitable for surgical repair. Patient radiation exposure, however, may be affected by pre-procedural factors such as: Gender, BMI, and anatomic tumor characteristics including tumor size and multinodular disease.

Current literature assessing TACE radiation exposure has reported a varied range of radiation doses according to RAK and KAP. The previous studies have reported radiation doses ranging between 220 and 9528 mGy, according to RAK.[2,17] Other studies have used KAP to report radiation dose. According to these studies, radiation exposure may range between 73.5 Gy*cm^2 and 767.2 Gy*cm^2.[18] In our series, KAP and RAK values are within the ranges of the previous reports. Likewise, both parameters were significantly affected by pre-procedural characteristics. According to the previous authors, main reasons for radiation doses

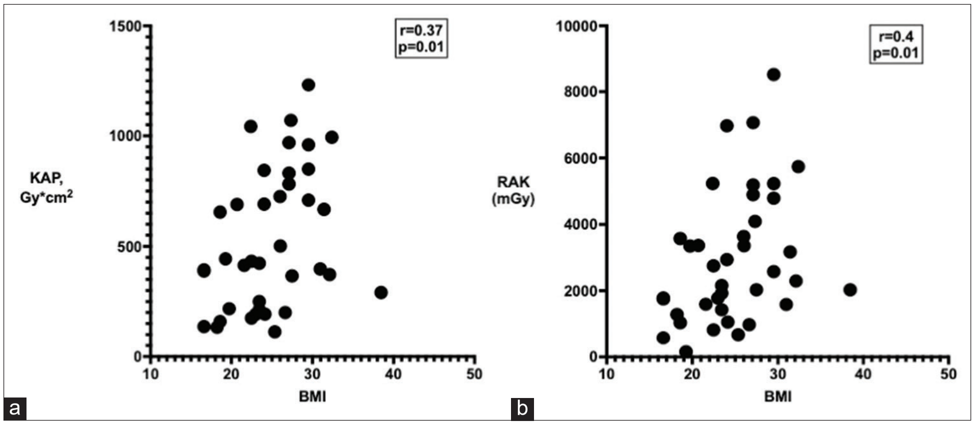

Figure 4: (a) Correlation between body mass index (BMI) and KAP. (b) Correlation between BMI and RAK.

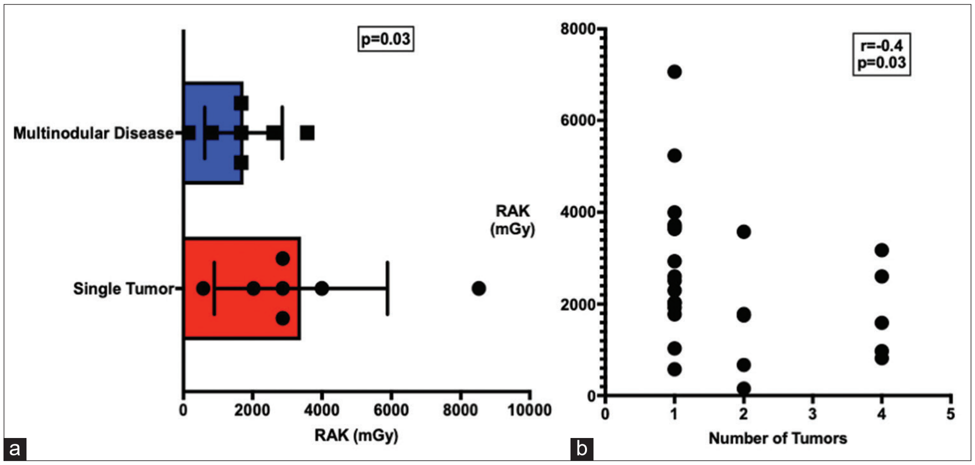

Figure 5: (a) Patient radiation dose by multinodular disease. (b) Correlation between RAK and number of tumors.

variations are related to the diversity of their populations and fluoroscopy equipment parameters.[18,19]

In a previous study, Garzon *et al.*[18] found that gender is an independent predictor of radiation dose, according to KAP. In this study, patients were divided in two groups based on the fluoroscopy equipment used for TACE. In both groups, men received higher radiation doses. In the same study, increased radiation doses were observed in patients with higher BMIs.[18] In a different study, Dauer *et al.* found a significant correlation between BMI and KAP with a positive r^2 value of 0.7 ($P < 0.01$).[17] In our study, similar results were found. Men received higher radiation doses according to RAK and KAP. Similarly, patients with higher BMIs were found to receive increased radiation dose, according to KAP. In our population, men were taller and heavier than women but only height was associated with radiation dose [Table 1]. Therefore, men having major exposure surface were exposed to higher radiation dose, according to KAP. To avoid higher radiation exposure, gender and anthropometric measurements should be considered before treating patients with HCC, especially if patients may require more than one embolization.

To reduce radiation dose during TACE, Kohlbrenner *et al.*[12] assessed the impact of using new image acquisition and processing platform employing a noise-reduction algorithm optimizing equipment settings including increased beam filtration without affecting image quality. Intraoperative system settings included a tube voltage of 80 kVp, a 0.7-mm focal spot and a large field of view (FOV) digital subtraction angiography (DSA) acquisition of 30 × 38 cm. Noise-reduction systems included a supplemental copper and aluminum filtration. The use of this new imaging platform resulted in a 45.9% reduction of the mean KAP and a 32.8% of the mean RAK when compared to standard imaging settings.[12] In our study, similar equipment settings were used with a large mean FOV of 42 cm and a mean tube voltage of 85 kVp [Table 1]. Similarly, imaging collimation was used in all procedures following low dose mode standards. According to our results, higher tube voltage resulted on a weak correlation with RAK and no correlation with KAP. As expected, higher radiation doses were observed when an increased number DSA series was required. This may be the case of challenging procedures with complex anatomy. The use of supplemental filtration was not available at our institution during the study period and it might be an important instrument to reduce radiation exposure, especially treating tumors with complex anatomy.

The previous studies have not analyzed the association between technical complexity and patient radiation dose.[6,9] Technical recommendations for TACE, however, are currently based on the assessment of anatomic tumor characteristics. Number of tumors, tumor size, and tumor location are important parameters on the selection of the embolization agent and selective assessment of tumors.[6] A standard recommendation for TACE is the use of microcatheters for super selective catheterization of single and small tumors.[9] In our study, anatomic tumor characteristics were also used to assess the impact of technical TACE complexity on patient radiation dose.

Our analysis included multinodular disease and tumor size. According to our results, tumor size demonstrated a weak positive correlation with RAK. Interestingly, number of target tumors revealed a significant negative correlation with radiation dose. Furthermore, patients with multinodular disease demonstrated a 10% radiation dose decrease compared to patients with a single tumor. Similarly, patients with multinodular disease required a lower number of DSA series with a lower radiation dose.

We believe that the reduction on radiation dose in patients with multinodular disease is explained by the use of staged treatment of multiple tumors (80% of the patients with multiple tumors were staged), and/or the use super selective catheterization of single small tumors. In fact, patients with multinodular disease and staged repair required a lower number of DSA series per embolization session.

We believe that in patients treated with staged repair, the use of diagnostic pre-embolization DSA series is reduced by the use of the previous angiography images on the assessment of tumor vascular anatomy and on the definition of the embolization plan. The use of additional embolization sessions, however, increases cumulative radiation dose. Therefore, a further study that assesses biologic effects of cumulative radiation after multiple TACE sessions is required.

A reasonable number of limitations were observed in this study. The first limitation is related to the observational design of the study. To avoid bias related to the retrospective nature of our study, only patients treated with the same fluoroscopy equipment and standard X-ray technical parameters were included in the study. A second limitation is a small sample size of the study. To prevent lack of reproducibility related to sample size, logarithmic transformation was performed to analyze associations using parametric tests. In addition, simple regression analysis was performed to assess the impact of anatomic characteristics on radiation dose. Multiple regression analysis, however, failed to demonstrate statistical significance. Therefore, further studies with larger simple sizes are required to perform multivariate analysis that assesses the impact of other technical and anatomic predictors of radiation during TACE. Similarly, further studies are required to assess the impact of anatomic tumor characteristics and technical factors on personal interventional-staff radiation dose.

CONCLUSION

TACE is an effective method to treat patients with HCC that may be performed within acceptable radiation dose limits. Anatomic tumor characteristics were found to be associated with patient radiation dose. Interestingly, multinodular disease was found to cause a radiation dose reduction of 10%. This may be related to the use of staged repair in patients with multinodular disease. Further studies are required to validate these findings.

Main points

- Patients with HCC may be treated with TACE using ionizing radiation without exceeding published radiation limits by the routine use of low dose mode settings on fluoroscopy equipment.
- Baseline patient characteristics affect radiation dose during TACE. Male gender and higher BMI are associated with higher radiation doses.
- Procedure complexity by anatomic tumor characteristics was found to affect patient radiation dose. Patients with larger tumors were found to receive higher radiation doses.
- Interestingly, patients with multinodular disease received lower radiation doses compared to patients with single tumors. These variations on radiation doses may be associated to the staging protocol of patients with multinodular disease.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Patel AP, Gallacher D, Dourado R, Lyons O, Smith A, Zayed H, *et al.* Occupational radiation exposure during endovascular

aortic procedures. Eur J Vasc Endovasc Surg 2013;46:424-30.
2. Miller DL, Balter S, Cole PE, Lu HT, Berenstein A, Albert R, *et al*. Radiation doses in interventional radiology procedures: The RAD-IR study: Part II: Skin dose. J Vasc Interv Radiol 2003;14:977-90.
3. Miller DL, Kwon D, Bonavia GH. Reference levels for patient radiation doses in interventional radiology: Proposed initial values for U.S. practice. Radiology 2009;253:753-64.
4. Kirkwood ML, Arbique GM, Guild JB, Timaran C, Chung J, Anderson JA, *et al*. Surgeon education decreases radiation dose in complex endovascular procedures and improves patient safety. J Vasc Surg 2013;58:715-21.
5. Kirkwood ML, Chamseddin K, Arbique GM, Guild JB, Timaran D, Anderson JA, *et al*. Patient and operating room staff radiation dose during fenestrated/branched endovascular aneurysm repair using premanufactured devices. J Vasc Surg 2018;68:1281-6.
6. Miura JT, Gamblin TC. Transarterial chemoembolization for primary liver malignancies and colorectal liver metastasis. Surg Oncol Clin N Am 2015;24:149-66.
7. Lo CM, Ngan H, Tso WK, Liu CL, Lam CM, Poon RT, *et al*. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. Hepatology 2002;35:1164-71.
8. Llovet JM, Real MI, Montana X, Planas R, Coll S, Aponte J, *et al*. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: A randomised controlled trial. Lancet 2002;359:1734-9.
9. Raoul JL, Sangro B, Forner A, Mazzaferro V, Piscaglia F, Bolondi L, *et al*. Evolving strategies for the management of intermediate-stage hepatocellular carcinoma: Available evidence and expert opinion on the use of transarterial chemoembolization. Cancer Treat Rev 2011;37:212-20.
10. Marelli L, Stigliano R, Triantos C, Senzolo M, Cholongitas E, Davies N, *et al*. Transarterial therapy for hepatocellular carcinoma: Which technique is more effective? A systematic review of cohort and randomized studies. Cardiovasc Intervent Radiol 2007;30:6-25.
11. Lau WY, Yu SC, Lai EC, Leung TW. Transarterial chemoembolization for hepatocellular carcinoma. J Am Coll Surg 2006;202:155-68.
12. Kohlbrenner R, Kolli KP, Taylor AG, Kohi MP, Fidelman N, LaBerge JM, *et al*. Patient radiation dose reduction during transarterial chemoembolization using a novel x-ray imaging platform. J Vasc Interv Radiol 2015;26:1331-8.
13. Takayasu K, Arii S, Kudo M, Ichida T, Matsui O, Izumi N, *et al*. Superselective transarterial chemoembolization for hepatocellular carcinoma. Validation of treatment algorithm proposed by Japanese guidelines. J Hepatol 2012;56:886-92.
14. Hendee WR, Edwards FM. ALARA and an integrated approach to radiation protection. Semin Nucl Med 1986;16:142-50.
15. The 2007 recommendations of the international commission on radiological protection. ICRP publication 103. Ann ICRP 2007;37:1-332.
16. Fletcher DW, Miller DL, Balter S, Taylor MA. Comparison of four techniques to estimate radiation dose to skin during angiographic and interventional radiology procedures. J Vasc Interv Radiol 2002;13:391-7.
17. Dauer LT, Thornton R, Boylan DC, Holahan B, Prins R, Quinn B, *et al*. Organ and effective dose estimates for patients undergoing hepatic arterial embolization for treatment of liver malignancy. Med Phys 2011;38:736-42.
18. Garzon WJ, Kramer R, Khoury HJ, de Barros VS, Andrade G. Estimation of organ doses to patients undergoing hepatic chemoembolization procedures. J Radiol Prot 2015;35:629-47.
19. Aroua A, Rickli H, Stauffer JC, Schnyder P, Trueb PR, Valley JF, *et al*. How to set up and apply reference levels in fluoroscopy at a national level. Eur Radiol 2007;17:1621-33.

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