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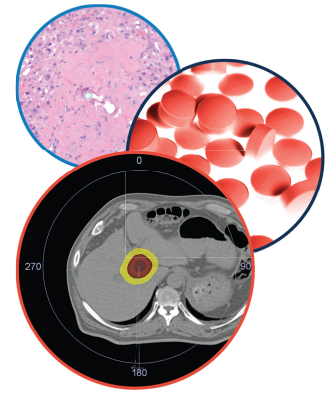

Hepatic Oncology

Pathological complete response with immunotherapy and brachytherapy to 15 metastatic liver lesions in a single patient

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Materials & methods: High dose rate interstitial brachytherapy (HDR-IBT) treatment plan for 15 metastatic liver lesions in a patient with pancreatic cancer was retrieved and analyzed for liver dose parameters and diaphragm dose. Serial ^{18}F-FDG PET-CT scans were reviewed for disease response assessment and left liver lobe volume. Serial laboratory records were analyzed for liver parameters. **Results:** Left liver lobe volume increased from 241 cm^3 pre-HDR-IBT to estimated 600 cm^3 after seven sessions of HDR-IBT. Metabolic complete response (CR) and subsequently pathological CR was confirmed in the right hepatotectomy specimen for all the 15 PET-CT avid lesions treated with HDR-IBT. Maximum diaphragm dose in a single fraction was 82 Gy. The liver parameters were stable and patient did not develop radiation induced liver disease. **Discussion:** This is the largest reported series of HDR-IBT to liver lesions in a single patient. This first ever reported combined treatment of immunotherapy (IT) and HDR-IBT had likely rendered this patient disease free both at local the liver and systemically. Metabolic CR by PET-CT can be seen as early as 46 days after HDR-IBT. Diaphragm can tolerate very high doses of radiation and repeated treatment. **Conclusion:** In this patient HDR-IBT for multiple liver lesions with IT is well tolerated. PET-CT can be used for response assessment of HDR-IBT liver. Synergistic effect of IT with HDR-IBT and it's role as bridging for liver resection has clinical potential and should be further studied in prospective trials.

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Keywords: brachytherapy and immunotherapy • diaphragm radiation tolerance • HDRIBT liver • liver brachytherapy • Pet-CT for brachytherapy response

Pancreatic adenocarcinomas (PAC) is known to have a dismal prognosis with 1 year survival of 24.8% for males and 26.2% for females for all stages [1]. Even with the newer regimens such as FOLFIRINOX, the median overall survival in metastatic pancreatic cancer patient has only improved from 6.8 to 11.6 months [2]. Currently, there is a great interest in the use of immunomodulatory agents to improve outcomes in the metastatic PAC patients either as single agent or in combination [3]. Most patients with pancreatic cancer succumbed to the disease due to systemic relapse, especially in the liver which is commonest site of distant metastasis. Furthermore, patient whose initial recurrence is in liver fare badly compared with those with initial recurrence in the lung [4]. Although, liver resection has been shown to improve the outcomes in patients with limited liver metastatic disease from colorectal cancers, there is very little evidence in the literature for metastatic cancers from other sites, such as PAC [5]. Most patients with liver metastasis are not surgical candidates and high dose rate interstitial brachytherapy (HDR-IBT) has been used as one of the non surgical local liver directed therapy in liver metastasis from various organs with local control rates ranging from 70 to 100% [6,7].

Future Medicine

This manuscript describes the clinical outcome in a single patient who successfully underwent a series of seven HDR-IBT procedures to 15 metastatic liver lesions over a period of 7 months followed by hemi-hepatectomy which revealed no residual tumor cells. Liver dose statistics over the staggered HDR-IBT, HDR-IBT acting as bridging for subsequent liver resection, likely tolerance dose of the diaphragm, the role of concurrent immunotherapy (IT) and the complexity of interpreting the 18-fluorodeoxyglucose (^{18}F-FDG) PET-CT findings after both HDR-IBT and IT is discussed here.

Case history

A fit 60-year-old gentleman underwent pancreaticoduodenectomy for a 3 cm moderately differentiated head of pancreas ductal adenocarcinoma (TNM8 pT2pN0M0, stage 1B) which was complicated by pancreatocojejunostomy leakage requiring prolonged ICU admission. His Ca19-9 was fluctuating (18–30 U/ml) within the normal the range and was not helpful in the clinical monitoring, while CEA was not raised throughout the disease course.

A PET-CT performed 2 months after the surgery showed an ^{18}F-FDG -FDG avid solitary para-aortic lymph node (PAN), measuring 1.1 cm and maximal standardized uptake value (SUV_{max}) of 7.7. He was then commenced on doublet chemotherapy with intravenous (iv.) gemcitabine 800 mg/m^2 on day 1, day 8 and oral capecitabine 825 mg/m^2 twice daily for 14 days, which was repeated every 21 days. Reassessment PET-CT after six cycles chemotherapy showed no ^{18}F-FDG avid disease. Thereafter, he received adjuvant external beam radiotherapy (EBRT) to the tumor bed and PAN region to a dose of 50.4 Gy in 28 fractions using the intensity modulated radiation therapy technique concurrent with oral capecitabine 1 g twice daily.

Unfortunately, a surveillance PET-CT in January 2020 (11 months after the diagnosis) showed five ^{18}F-FDG avid liver lesions suggestive metastasis and no distant metastasis. As patient was traumatized with the previous post operative complications, scanty evidence in the literature for liver resection in this clinical scenario and also the lesions are multicentric in the right lobe with minimal left lobe reserve, surgical options were ruled out at that point and the option of HDR-IBT was given to the patient.

HDR-IBT series to 15 metastatic liver lesions, IT & right hemi-hepatectomy

HDR-IBT to the 5 ^{18}F-FDG avid lesions was performed over two sessions 1 week apart. Thereafter, over a period of 7 months, the patient underwent a total of seven sessions of HDR-IBT, treating 15 lesions in multiple segments of right lobe of liver. The summary PET-CT findings, HDR-IBT procedures and surgery with their respective dates are illustrated in Figure 1. The technique of HDR-IBT liver is described in another publication [8]. The HDR-IBT plans with prescribed dose of 20 Gy in single fraction covering the periphery of the tumor for all 15 lesions and the maximum intensity projection serial PET-CT images from April 2019 till December 2020 are shown in Figure 2A & B. Vigilance was used during HDR-IBT treatment planning in ensuring that the left lobe of liver is well spared from the radiation dose.

PET-CT after four sessions of HDR-IBT treating eight lesions (Figure 1) showed 5 new ^{18}F-FDG avid lesions limited to the right lobe of liver and all the previous HDR-IBT treated lesions having complete metabolic response. Next generation multigene sequencing at this point showed PDL1- 45% with no nuclear loss of MLH1, MSH2, MSH6 and PMS2. Due to the systemic nature of the disease, after multidisciplinary discussion, patient was commenced on PDL-1 check point inhibitor (iv. pembrolizumab 100 mg every 21 days) and further HDR-IBT to the new liver lesions was withheld. An early PET-CT after 2 cycles of pembrolizumab (6 weeks later) revealed another 2 new ^{18}F-FDG avid lesions in the right lobe of liver and also increased ^{18}F-FDG avidity of the previously seen five lesions. Otherwise, all the HDR-IBT treated liver lesions showed no significant ^{18}F-FDG avidity.

With limited systemic therapy options, insufficient left lobe reserve for hemi hepatectomy [Figure 3], reasonably small size of the ^{18}F-FDG avid lesions coupled with good liver blood parameters (Figure 4A & B) the option of targeted HDR-IBT to all the seven lesions was discussed with the patient giving benefit of doubt on the possibility of pseudo progression due to IT. Patient underwent three more sessions of HDR-IBT to the seven lesions in the right lobe of liver. The 3 weekly pembrolizumab was continued during and after the liver HDR-IBT for a total of seven cycles (Figure 1).

The intensity modulated radiation therapy and HDR-IBT dose statistics to the liver and the HDR-IBT dose statistics to the right hemi-diaphragm is shown in Table 1. The HDR-IBT treatments were well tolerated with fever lasting less than 24 h and localized liver capsular pain being the main complaint. The pre procedure assessment, HDR-IBT procedure, dose constraints and post-treatment monitoring is based on the IPPT-USM Liver Brachytherapy Protocol 2019 which was adopted with permission from Konrad M *et al.* 2016 [9].

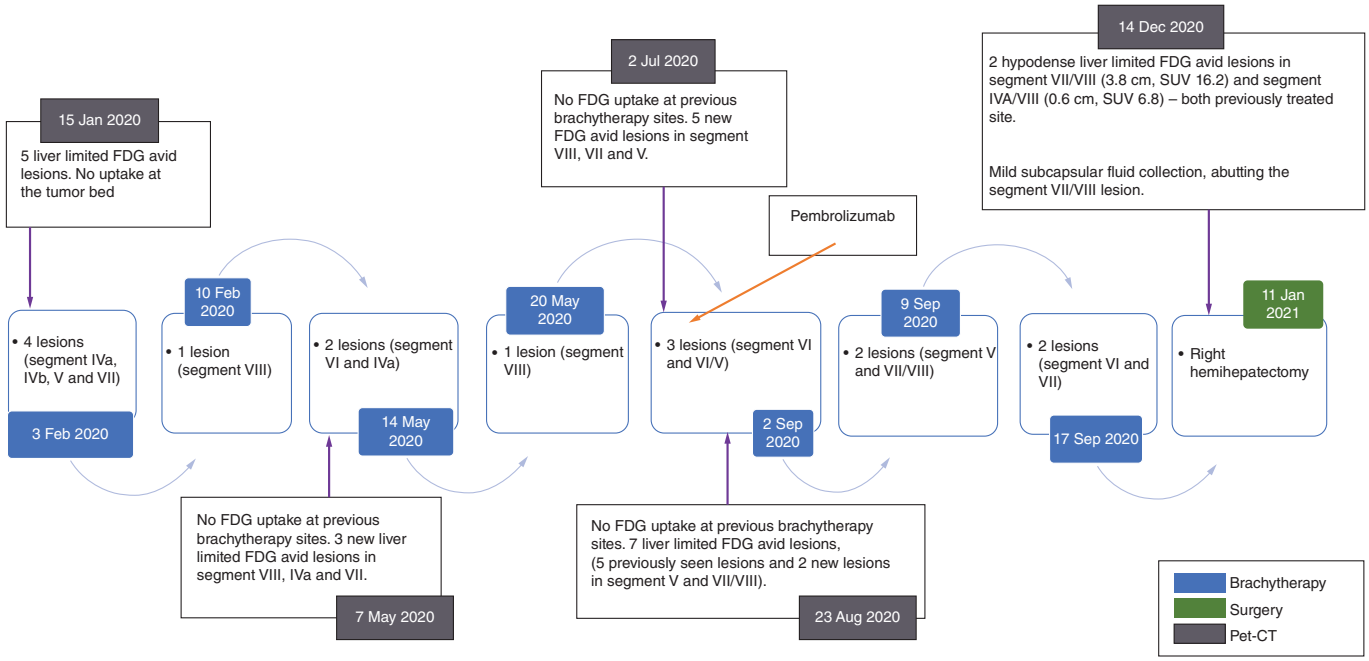

Figure 1. Timeline showing the PET-CT scan, high-dose rate interstitial brachytherapy liver for the 15 lesions and surgery.

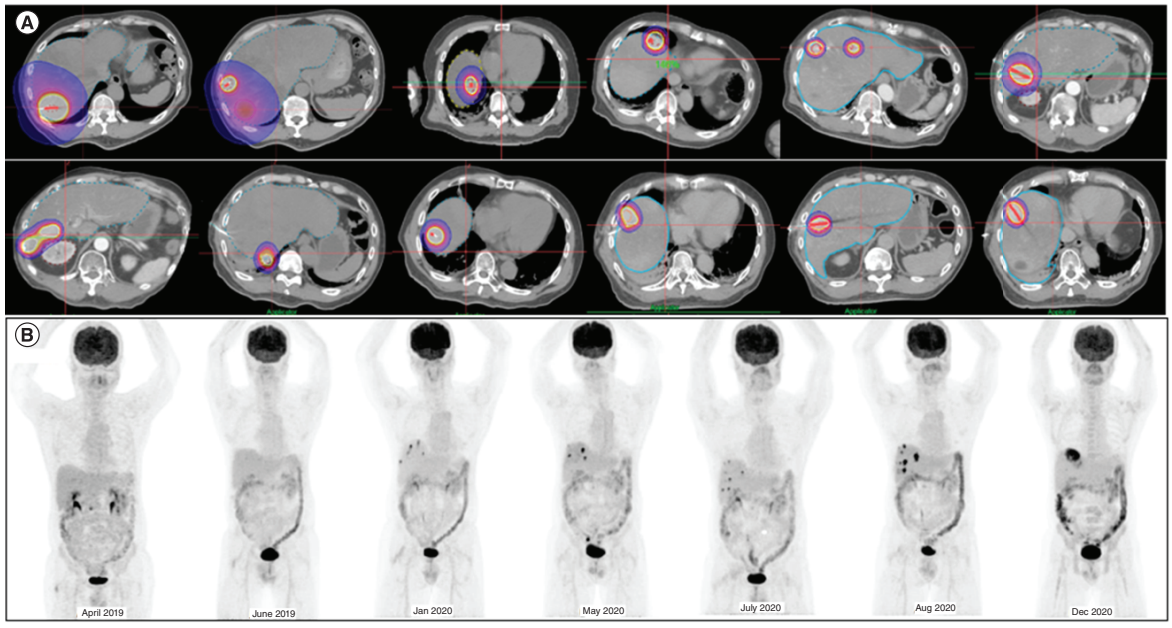

Figure 2. High-dose rate interstitial brachytherapy plans of the 15 lesions treated (A) and the maximum intensity projectionimages of ^{18}F-^{18}F-FDG PET-CT performed serially from April 2019 till December 2020 (B).

Re-evaluation PET-CT after completing seven cycles of pembrolizumab in December 2020 showed an FGD avid segment VII/VIII lesion measuring 3.0 × 3.8 cm with SUV_{max} 16.2 (Figure 5A) and another smaller ^{18}F-FDG avid adjacent lesion in segment VIII/IVA (0.6 × 0.5 cm with SUV_{max} 6.8). Both the lesions were at previously treated area and showed central necrosis. There was subcapsular fluid collection at the right perihepatic region in continuity with the current larger ^{18}F-FDG avid lesion suggestive of post brachytherapy reactive changes. No other ^{18}F-FDG avid disease was seen in the liver or elsewhere.

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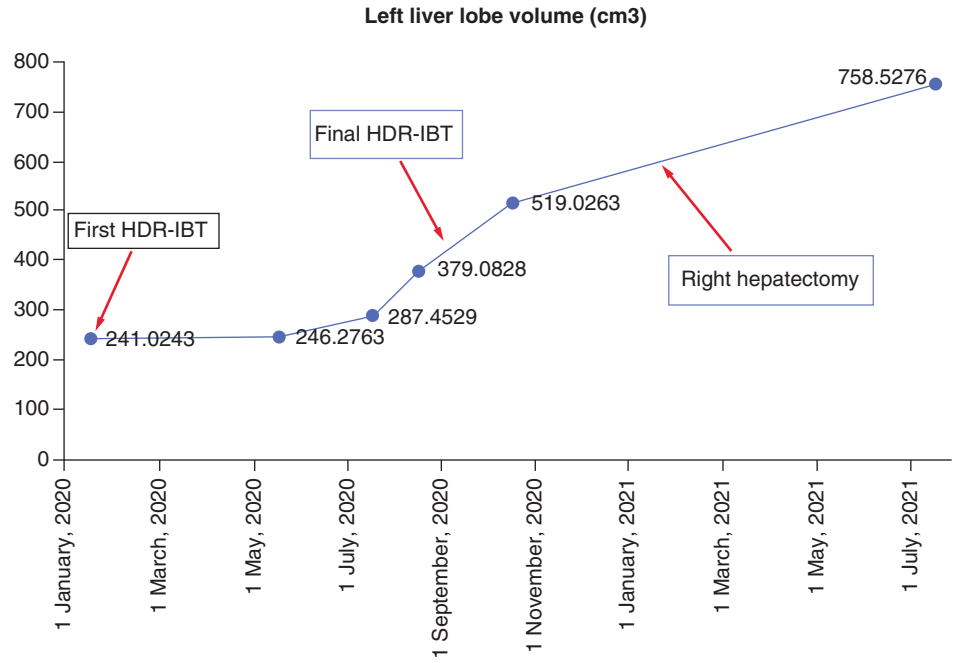

Figure 3. Changes in left lobe liver volume.
HDR-IBT: High-dose rate interstitial brachytherapy.

Table 1. Dose statistics to the liver and diaphragm for the seven fractions of high-dose rate interstitial brachytherapy to liver and external beam radiotherapy to pancreatic bed.

	Liver			Diaphragm			
	5 Gy (%)	8 Gy (%)	10 Gy (%)	0.2 cc (Gy)	0.5 cc (Gy)	EBRT (3-Aug-19) liver dose	
3 February	34.46	21.93	17.31	40.26	37.28	Mean	12.93 Gy
10 February	5.81	3.28	2.44	24.5	21.29	V_{15Gy}	30.27%
14 May	11.71	5.17	3.68	4.25	3.78	V_{20Gy}	26.12%
20 May	9.43	4.99	3.68	84.28	57.29	V_{30Gy}	16.36%
2 September	21.67	12.29	10.21	3.13	3.13	V_{40Gy}	7.57%
9 September	12.73	7.43	5.725	49.46	34.19		
17 September	15.2	8.76	6.576	22.1	16.57		

EBRT: External beam radiotherapy.

At this point the disease free left lobe of liver has significantly hypertrophied which made it possible for the consideration of liver resection as shown in Figure 3. The liver parameters were within reasonable range, with only the total bilirubin slightly above the upper normal limit and alkaline phosphatase 2.5-times upper normal range.

Patient underwent right hemi-hepatectomy on 11 January 2021 (Figure 5B). He recovered well after 6 weeks of antibiotics for infected biloma post operatively. Histopathological examination of the resected right lobe of liver found two foci of abscess and infarcted liver tissue with no viable tumor cell being identified. Surveillance CT scan and CA19.9 levels at 5, 11, 14 and 18 months later in (June 2021 till July 2022) showed no evidence of local or distant metastasis and patient is currently back to his daily routine and work as a private dentist.

Discussion

After extensive literature search, we found this manuscript to have the largest HDR-IBT liver series in a single patient to be reported. This is a unique case of a patient with metastatic pancreatic carcinoma whose metastatic disease is limited to right lobe of liver only. He has been in disease remission for past 18 months; 40 months after initial diagnosis and 30 months since the diagnosis of liver metastasis.

This manuscript is unique in sense that it contributes to the incomplete science in the world literature on the:

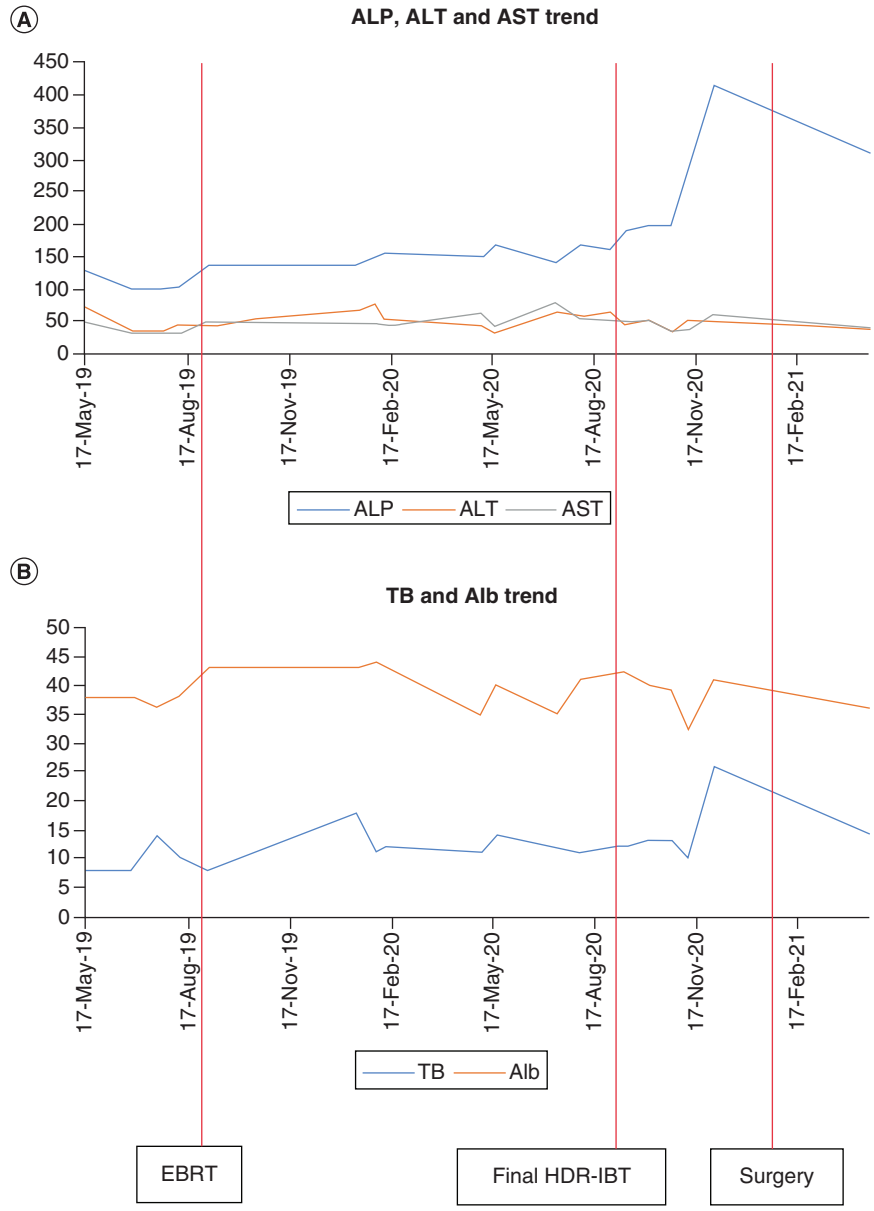

Figure 4. Trends of AST, ALP and ALT (A) and total bilirubin, albumin (B).
AST: Aspartate aminotransferase; ALP: Alkaline phosphatase; ALT: Alanine transaminase.

- Role of liver HDR-IBT as a bridging for liver resection.
- Role of IT in combination with brachytherapy.
- Use of PET-CT for HDR-IBT response assessment.
- Ability for one lobe of liver to withstand very high doses of staggered radiation without the patient going into radiation induced liver disease if at least one lobe is well spared.
- Radiation tolerance of the diaphragm.

Comparison of different modality as bridging for liver transplantation between stereotactic body radiotherapy (SBRT), trans-arterial chemoembolization and radiofrequency ablation (RFA) showed no difference in the transplant rates [10]. Radio-embolization has also been used as a bridging for surgery [11]. HDR-IBT for metastatic liver lesions especially for non-colorectal primary has local control rates similar to RFA, while possessing extra advantage when treating lesions larger than 3 cm, lesions at the proximity of biliary tree or near the diaphragm and also near large blood vessels whereby the heat sink effect is a known limitation with RFA [12–15]. Despite these clear

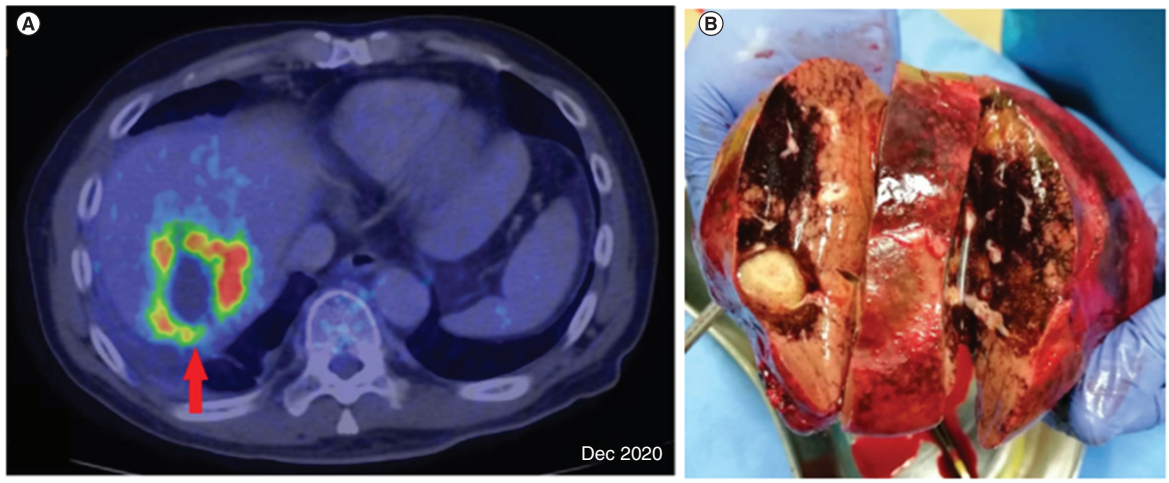

Figure 5. Fused PET-CT axial image demonstrates a larger metabolically active lesion in segment VII/VIII with central necrosis (red arrow) (A) and right hepatectomy specimen (B).

advantages, there is no published report on the use of HDR-IBT liver as the bridging for surgery. In this patient, the intentionally spared left liver lobe volume increased from 241 cm^3 before the first HDR-IBT fraction to an estimate of 600 cm^3 1 year later before undergoing right hepatectomy.

The abscopal effect of radiation therapy (tumor regression at non-irradiated sites) is increasingly being recognized in the SBRT setting. Popp *et al.* extensively reviewed this immune mediated process which is radiation dose per fraction dependent and is further enhanced by the addition of IT or immune check point inhibitors [16]. The clinical outcome and the toxicity of this this approach of combining SBRT with IT has been tested in many clinical trials involving the metastatic solid tumors [17,18]. There is an interesting recent article in the brachytherapy by Patel et. al. on the cooperative mechanism and clinical opportunity of combining brachytherapy and IT. Patel *et al.* summarized the diverse mechanism by which radiation therapy may elicit immunomodulatory effect based on four dose regions – very high, intermediate (8–12 Gy), moderate and low dose (1–2 Gy) region. Unlike the more homogenous EBRT dose distribution, physical property of HDR-IBT invariably produce a heterogeneous treatment plan that can be ideal for this phenomenon to occur [19]. Despite this sound scientific concept, to our knowledge there is no published report on the use of IT concurrent with brachytherapy and this manuscript is the first of it's kind on this issue. While this patient had a PDL1 expression of 45% in the tumor cells, the usefulness of the PDL-1 assay to predict the treatment response to immune check point inhibitors is still an area of contention [20]. Seven cycles of pembrolizumab concurrent with HDR-IBT to 15 lesions over seven sessions was well tolerated in this patient. While this single patient report maybe insufficient to conclusively confirm the benefit of this combined approach, this manuscript shows that it is a clinical feasible.

The only published report in literature on the use of PET-CT for liver HDR-IBT response assessment showed no significant SUV uptake 6 months after 12 Gy of peripheral dose to a single liver metastatic lesion from stomach cancer. Response assessment with PET-CT for thermal ablation procedure like RFA may not be applicable to HDR-IBT due to the differences in the mechanism of cell kill [21]. Extrapolation from the published liver or lung SBRT series is saddled with the presence of radiation pneumonitis mimicking recurrence and the non-uniform timing of the PET-CT complicating the interpretation. The interval between the last fraction of brachytherapy to PET-CT that showed complete metabolic response in the treated lesions this patient range from as early as 43–88 days. The two metabolically active areas seen in the last PET-CT in December 2020 were the sites treated with HDR-IBT 7 and 10 months earlier with dose overlaps from subsequent HDR-IBT treatment from adjacent lesions which was later confirmed by histopathological studies not to harbor any malignant cells. Retrospectively looking, high index of suspicion for liver infection should have been there given that the preceding scans were negative and normal CA19.9 levels, while it is known that CA19.9 may not be of significant value in detecting recurrence, given the reported specificity and sensitivity of CA19.9 in pancreatic adenocarcinoma at 78.2% (95% CI: 76.1–80.2%) and 82.8% (79.9–85.3%) respectively [22].

Pseudo progression in PET-CT is a rather complex issue with IT that may lead to premature withdrawal of effective treatment [23]. As pseudo progression was highly suspected in this case, treatment with IT was continued in addition to aggressive liver directed therapy using HDR-IBT to the isolated liver lesions.

The commonly used dose constraint in liver HDR-IBT of 1/3 of liver volume to receive less than 5 Gy of radiation was well respected for each of the seven sessions of brachytherapy [9]. This estimate of liver tolerance is probably rather conservative and the true tolerance of a single liver subunit may be as high as 10 Gy in single fraction and repeated HDR-IBT treatments to small volume of overlapping region can be safely given [24]. However, bearing in mind on the likelihood of further need for HDR-IBT extreme care was taken during the applicator insertion and treatment planning process to keep the radiation dose to the left lobe near negligible. The ability to save one lobe of liver completely while treating 15 metastatic lesions is a unique characteristic of HDR-IBT that cannot be achieved by other radiation modality such as SBRT. The diaphragm in this patient received significant dose – as high as 84 Gy in single session and there was also dose overlap with subsequent HDR-IBT. Except for the fibrotic changes intra-operatively, there were no signs of impending perforation noted. This further confirms the understanding among brachytherapist that diaphragm being a muscle can tolerate very high doses of radiation and treatment of subdiaphragmatic liver tumors in segment VII/VIII which maybe an issue with other ablative procedures like RFA is very much feasible using HDR-IBT. The details of the cumulative liver and diaphragmatic dose with the cumulative EBRT dose for this series will be reported in another planned technical publication as it is beyond the scope of this manuscript.

Conclusion

HDR-IBT for 15 liver lesions over seven sessions with concurrent IT was well tolerated in this patient. PET-CT can be used for response assessment of HDR-IBT liver and complete response can be seen as early as 43 days. Synergistic effect of IT with HDR-IBT and it's role as bridging for liver resection has clinical potential and should be further studied in prospective trials.

Summary points

- The high dose rate interstitial brachytherapy (HDR-IBT) treatment plan for 15 metastatic liver lesions in a patient with pancreatic cancer was retrieved and analyzed for liver dose parameters and diaphragm dose.
- Serial ^{18}F-FDG PET-CT scans were reviewed for disease response assessment and left liver lobe volume.
- Serial laboratory records were analyzed for liver parameters.
- Left liver lobe volume increased after seven sessions of HDR-IBT.
- Metabolic complete response and subsequently pathological complete response was confirmed in the right hepatotectomy specimen for all 15 PET-CT avid lesions treated with HDR-IBT.

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Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

Informed consent was obtained from the patient described in this manuscript and has institutional human ethics approval for CT-guided interstitial liver brachytherapy analysis in Universiti Sains Malaysia (JEPeM USM Code: USM/JEPeM/20050263).

References

Papers of special note have been highlighted as: • of interest; •• of considerable interest

1. Cancer Research UK. Pancreatic cancer mortality statistics. https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/pancreatic-cancer/survival#heading-Zero
2. Conroy T, Desseigne F, Ychou M *et al.* FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N. Engl. J. Med.* 364(19), 1817–1825 (2011).
3. Schizas D, Charalampakis N, Kole C *et al.* Immunotherapy for pancreatic cancer: a 2020 update. *Cancer Treat. Rev.* 86, 102016 (2020).
4. Sahin IH, Elias H, Chou JF, Capanu M, O'reilly EM. Pancreatic adenocarcinoma: insights into patterns of recurrence and disease behavior. *BMC Cancer* 18(1), 769 (2018).
5. Kanas GP, Taylor A, Primrose JN *et al.* Survival after liver resection in metastatic colorectal cancer: review and meta-analysis of prognostic factors. *Clin. Epidemiol.* 4, 283–301 (2012).
6. Collettini F, Gebauer B. CT-guided high dose rate brachytherapy ablation of liver metastases. *Imag. Med.* 5, 383–388 (2013).
7. John RG, Ho F, Appalanaido GK *et al.* Can radiotherapy finally "go live" in the management of liver metastases? *Hep. Res.* 6, 56 (2020).
8. Appalanaido GK, Bahajjaj SIBZ-A, Shukor SA, Ahmad MZ, Francis HCH. Case report-staged brachytherapy achieving complete metabolic response in unresectable oligometastatic colorectal cancer to the liver. *Oxford Med.Case Rep.* 2021(4), 141–144 (2021).
9. Mohnike K, Wolf S, Damm R *et al.* Radioablation of liver malignancies with interstitial high-dose-rate brachytherapy: complications and risk factors. *Strahlenther. Onkol.* 192(5), 288–296 (2016).
10. Sapisochin G, Barry A, Doherty M *et al.* Stereotactic body radiotherapy vs. TACE or RFA as a bridge to transplant in patients with hepatocellular carcinoma. An intention-to-treat analysis. *J. Hepatol.* 67(1), 92–99 (2017).

• **Describes the use of local liver directed therapy as bridging for surgery.**

11. Braat AJaT, Huijbregts JE, Molenaar IQ, Borel Rinkes IHM, Van Den Bosch MaaJ, Lam MGEH. Hepatic radioembolization as a bridge to liver surgery. *Front. Oncol.* 4, 199 (2014).
12. Wieners G, Mohnike K, Peters N *et al.* Treatment of hepatic metastases of breast cancer with CT-guided interstitial brachytherapy – a Phase II-study. *Radiother. Oncol.* 100(2), 314–319 (2011).
13. Collettini F, Golenia M, Schnapauff D *et al.* Percutaneous computed tomography-guided high-dose-rate brachytherapy ablation of breast cancer liver metastases: initial experience with 80 lesions. *J. Vasc. Interv. Radiol.* 23(5), 618–626 (2012).
14. Geisel D, Denecke T, Collettini F *et al.* Treatment of hepatic metastases from gastric or gastroesophageal adenocarcinoma with computed tomography-guided high-dose-rate brachytherapy (CT-HDRBT). *Anticancer Res.* 32(12), 5453 (2012).
15. Tselis N, Chatzikonstantinou G, Kolotas C, Milickovic N, Baltas D, Zamboglou N. Computed tomography-guided interstitial high dose rate brachytherapy for centrally located liver tumours: a single institution study. *Eur. Radiol.* 23(8), 2264–2270 (2013).

• **Shows the safety and efficacy of brachytherapy in treating central tumors.**

16. Popp I, Grosu AL, Niedermann G, Duda DG. Immune modulation by hypofractionated stereotactic radiation therapy: therapeutic implications. *Radiother. Oncol.* 120(2), 185–194 (2016).
17. Bang A, Schoenfeld JD. Immunotherapy and radiotherapy for metastatic cancers. *Ann. Palliat. Med.* 8(3), 312–325 (2018).
18. Lubas MJ, Kumar SS. The combined use of SBRT and immunotherapy – a literature review. *Curr. Oncol. Rep.* 22(12), 117 (2020).

• **Describes the synergistic effect of SBRT and immunotherapy in cancer treatment.**

19. Patel RB, Baniel CC, Sriramaneni RN, Bradley K, Markovina S, Morris ZS. Combining brachytherapy and immunotherapy to achieve *in situ* tumor vaccination: a review of cooperative mechanisms and clinical opportunities. *Brachytherapy* 17(6), 995–1003 (2018).

•• **Describes the probability of brachytherapy inducing potent immune effect against tumor cells.**

20. Davis AA, Patel VG. The role of PD-L1 expression as a predictive biomarker: an analysis of all US Food and Drug Administration (FDA) approvals of immune checkpoint inhibitors. *J. Immuno. Ther. Cancer* 7(1), 278 (2019).
21. Aarntzen EHJG, Heijmen L, Oyen WJG. ^{18}F-FDG PET/CT in local ablative therapies: a systematic review. *J. Nucl. Med.* 59(4), 551–556 (2018).
22. Poruk KE, Gay DZ, Brown K *et al.* The clinical utility of CA 19-9 in pancreatic adenocarcinoma: diagnostic and prognostic updates. *Curr. Mol. Med.* 13(3), 340–351 (2013).
23. Ma Y, Wang Q, Dong Q, Zhan L, Zhang J. How to differentiate pseudoprogression from true progression in cancer patients treated with immunotherapy. *Am. J. Cancer Res.* 9(8), 1546–1553 (2019).
24. Rühl R, Lüdemann L, Czarnecka A *et al.* Radiobiological restrictions and tolerance doses of repeated single-fraction hdr-irradiation of intersecting small liver volumes for recurrent hepatic metastases. *Radiat. Oncol.* 5, 44 (2010).

•• **Shows that the radiation tolerance of a single hepatic sub unit is probably higher than our current understanding.**