A new proposal of utilizing intraoperative electron radiation therapy on the surface of liver to prevent postoperative liver metastasis of pancreatic cancer

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A B S T R A C T

Pancreatic cancer is a lethal cancer with high rate of liver metastasis worldwide, whereas its treatment choices are limited to a large extent. The limitation of current therapeutic strategies calls for an effective approach which can lower the postoperative liver metastasis rate in order to improve the overall prognosis and survival rate. Comprehensively considering the basic knowledge and clinical practice of tumor treatment worldwide, we proposed three points of hypotheses. Basically, the existing evidences indicated that tumor cells shedding from pancreatic cancer localized in the marginal liver preferentially through the Portal vein. Then, the percentage depth dose distribution of electron radiation is consistent with the marginal distribution of liver metastasis from pancreatic cancer. Based on the characteristics of liver metastasis of pancreatic cancer and the percentage depth dose of electron radiation, we provide a new propose of preventing postoperative liver metastasis in a way of prophylactic intraoperative electron radiation therapy on the surface of liver. Intraoperative electron radiation is relatively easy to control radiation dose and treatment area under direct vision, effectively inhibiting the metastasis and growth of cancer cells and preventing further deterioration of pancreatic cancer patients' condition. Therefore, this hypothesis has an important clinical significance for postoperative rehabilitation and improvement of patients' survival.

Introduction

Pancreatic cancer, though ranking the 13th in the incidence of malignant tumors, remains the 4th leading mortality according to the global statistics on malignant tumors released by WHO in 2014 [1].With incidence risen rapidly worldwide, pancreatic cancer is projected to be the 2nd leading cause of cancer-related deaths to 2030 [2]. As a highly lethal cancer, the overall 5-year survival rate is 8% for all stages included, falling to 3% in patients with advanced pancreatic cancer [3]. Although radical surgical resection is the only prospective treatment of long-term survival for patients with this disease and leads to significantly longer survival compared with other treatment options, the overall 5-year survival rate for postoperative patients remains only 15–20% [4].

The diagnosis and treatment technology of pancreatic cancer has been greatly enhanced due to the progress of surgery, chemotherapy, radiotherapy and targeted therapy, while evolution in pancreatic cancer has been slow and the overall prognosis has not been significantly improved [5,6]. Poor prognosis of pancreatic cancer patients is closely related to postoperative recurrence and metastasis within a short time [7], in which postoperative liver metastasis accounts for 40%–90% [8–10] as an independent factor for the prognosis [11]. According to guidelines and clinical practices, metastatic pancreatic cancer patients are generally recommended to palliative treatment by chemotherapy regimens [12,13]. However, theses regimens are paralleled with severe adverse effects damaging patients' quality of life [14,15] and no reported related long-term survival [16].

Although it remains unquestionable that pancreatic cancer with metastatic spread is a contraindication for resection [12], metastases resection or liver-directed therapies in liver metastatic situations has been performed by a few centers around the world [17–20] with partly conflicting results. Thus, the meaning of surgery for pancreatic cancer with metastatic spread remains unknown. In addition, local therapy and interventional therapy have emerged in recent years. Local therapy like local thermal ablation [21,22] and irreversible electroporation [23,24] plus interventional therapy like transcatheter arterial chemoembolization [25] and transcatheter arterial radioembolization [26,27] all are the treatment methods after liver metastasis, which either have limitations in utilization or uncertain specific therapeutic effects.

Therefore, there is an urgent need for development of novel, effective strategies aiming to advance current therapeutic possibilities of pancreatic cancer, considering reducing liver metastasis as a breakthrough.

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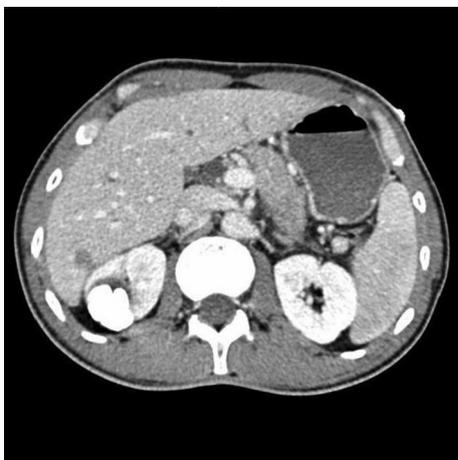 E-mail address: drmaxuelei@gmail.com (X. Ma).

Fig. 1. The CT image of a pancreatic cancer patient preoperatively shows marginal liver metastasis from a retrospective study in West China Hospital.

Hypothesis

Tumor cells shedding from pancreatic cancer localize in the marginal liver preferentially

Pancreatic cancer often metastasizes to distant organs like liver through blood vessels, with a particular distribution singly or multiply. A retrospective study, from January 2014 to January 2017 in West China Hospital, about CT images of 216 pancreatic cancer patients with liver metastasis preoperatively showed nearly 70% marginal liver metastasis (Fig. 1). This phenomenon, which has not been reported in depth before, prompted us to have a hypothesis about liver metastasis of pancreatic cancer in the following explanation.

As we all know, malignant cells not only grow invasively in the primary site, but also spread from the primary tumor and disseminate to distant sites to proliferate and form new tumor foci either singly or as cell clumps, actively or passively [28]. To form the process of metastases, tumor cells involve a series of sequential steps. Route of tumor spread involves invasion by the nature of the cell itself and penetration into blood vessels mainly depends on mechanical resistance [28–30]. Evidence suggests that tumor cells prefer to metastasize by veins because small and thin walled offer relatively less mechanical resistance, whereas arteries and arterioles are rarely invaded [28].Thus, pancreatic cancer cells, which have extremely strong permeability [31], are transferred to the liver through venous blood.

Some degree of adhesion and arrest of tumor cells within vessels occurs simply as a result of mechanical factors especially blood flow of target location [32]. For one thing, consistent with the anatomy evidence, veins in the pancreas drain into the splenic, the inferior and superior mesenteric vein, inflowing to the portal vein finally [33]. As the portal vein continues to drain into the hepatic vein as a percentage of 67% of liver blood supply [34], venous blood becomes less and more slowly when it branches repeatedly in the liver [35] (Fig. 2). For the other, liver sinusoid is formed by thin fenestrated and discontinuous membrane between blood and hepatocytes, which is easy for migration and extravasation [36]. Thus, venous blood slows down near the edge of the liver which brings benefits for pancreatic cancer cells' adhesion and migration in all probability.

In conclusion, we hypothesized that tumor cells shedding from pancreatic cancer preferred the liver margin through the portal vein.

The percentage depth dose distribution of electron radiation is consistent with the marginal distribution of liver metastasis from pancreatic cancer

As a complement of the treatment for cancer together with surgery and chemotherapy, radiotherapy has been highly cost-effective
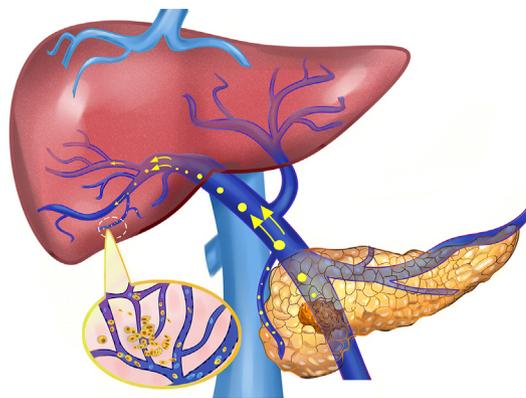

Fig. 2. Tumor cells shedding from pancreatic cancer localize in the marginal liver preferentially through the Portal vein.

accounting for merely 5% of the total cancer care cost [37].

Since the Curies discovered Radium and applied it to tumor therapy in 1896, tumor radiotherapy has had a history of more than 120 years. However, Radium, mostly used in brachytherapy at the initial stage of radiation [38], was abandoned due to the large amount of radiation to medical personnel. Nowadays, there are two types of tumor radiotherapy, photons radiation (X and gamma rays), which is widely used, and particle radiations (electron, neutron, proton and heavy ions rays) [39]. We can see how the percentage dose varies with depth (percentage depth dose) of different rays in Fig. 3 [40,41]. We can find that either X ray, gamma ray or neutron has a wide action range without a concentration of energy, resulting an inadequate or unsafe treatment. Protons and heavy ions are limited to high cost of cyclotrons, though offering a maximum destructive energy at the tumor site by a known Bragg's peak with a definite depth range [42].

For electron radiation, the percentage depth dose of 6, 9, 12, and 16 MeV electron energy is given in Fig. 3 [40,41]. According to Fig. 3 combined with the basic knowledge of tumor radiology, there are a few characters of electron radiation [40,43–45]. Firstly, there is a certain surface protection effect of percentage dose at 0 cm (surface dose) in a range of 75%-100%. Meanwhile, the lower the electron energy is, the lower the surface dose is. Secondly, as the electron energy increases, the plateau area, containing the maximum percentage dose with a relatively gentle depth change, will widens in depth. Thirdly, after the maximum percentage dose point, the percentage dose drops rapidly, especially for electron energy below 15 MeV, which is an important clinical characteristic. Furtherly, electron radiation from the decay of radioactive nuclei damages genetic material of cells, thus blocking their ability to divide and proliferate further with high energy [46]. Normal cells repair themselves to maintain its normal function status faster compared with tumor cells [47]. Combined with the above characteristics, numerous clinical applications have shown that electron radiation is commonly used in treating tumors close to body surface without penetrating deeply into tissues [39]. For instance, breast cancer is curable with radiation therapy accompanied by other modalities, in which local exposure to electron radiation is mainly used to reduce the recurrence and metastasis rate [48–50].

Thus, the use of electron radiation on liver offers a better dose distribution in tissues due to its unique dosage absorption feature consistent with the marginal distribution of liver metastasis from pancreatic cancer, minimizing the damage to liver capsule as well as deeper healthy tissues.

Prophylactic intraoperative 3 MeV electron radiation therapy on the surface of liver may prevent postoperative liver metastasis of pancreatic cancer

For patients with pancreatic cancer, only 15% −20% of them have the opportunity for receiving radical surgery in time when diagnosed
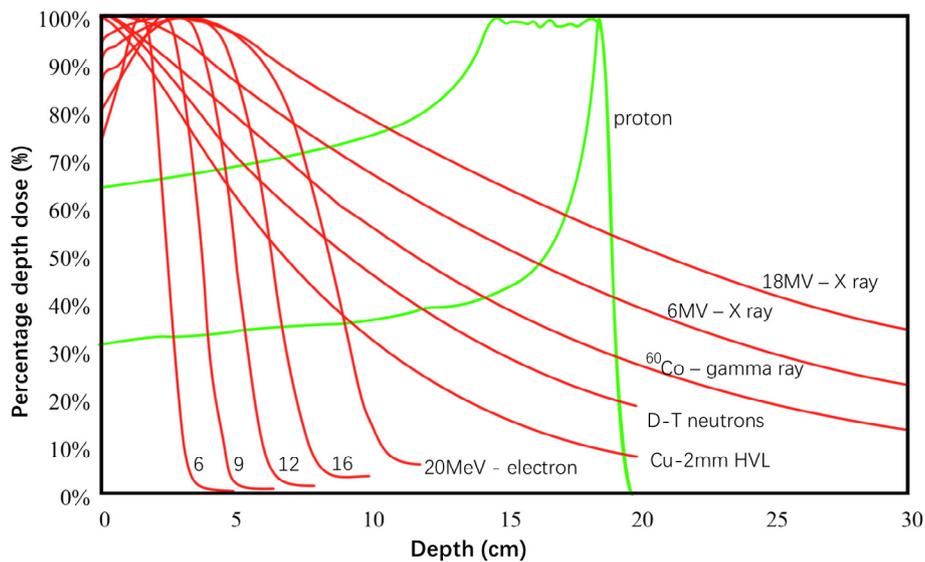
Fig. 3. The percentage depth dose of different rays, including electron ray (6, 9, 12, 16, 20 MeV), X ray(6MV, 8MV, Cu-2mmHVL), gamma ray (^{60}Co), neutron ray (D -T neutrons) and proton [36].

Fig. 4. Interoperation found tumor tissue of marginal liver metastasis from pancreas.

Fig. 5. Prophylactic intraoperative electron radiation prevents postoperative liver metastasis in pancreatic cancer patients with surgery indications.

cancer [51]. What's worse, even if R0 radical resection of pancreatic cancer is successfully implemented, the median survival time of patients is only 12–20 months, and the 5-year survival rate is still less than 20% [52]. Intraoperative manipulation as one of main factors affecting the spread of tumor cells, postoperative distant metastasis usually predicts a worse prognosis [48,49], in which liver metastasis accounts for the majority (40%–90%) [8–10] and occurs relatively early (about 5–11 months) [53]. However, there is a lack of effective treatment for pancreatic cancer with liver metastasis [54]. Similarly, the brain is a

frequent metastasis site of lung cancer, which is responsible for life threatening and survival shortening [55]. As for blood brain barrier is poorly penetrable for most drugs, prophylactic cranial irradiation is thought as a strategy to eliminate non-detectable brain metastases from lung cancer showing a decrease on the overall brain metastases rate [56,57]. Therefore, we try to apply prophylactic intraoperative electron radiation to pancreatic cancer patients with surgery indications, that is, without liver metastasis (Fig. 5).

To be more precise, the CT images of the retrospective study mentioned above (Fig. 1) and intraoperative probes of patients with liver metastasis (Fig. 4) showed that the depth of marginal liver metastasis was ≤1 cm primarily. Basically, energy value, therapeutic apparatus structure, and various substances along the path will affect the percent depth dose curve of the electron radiation [40]. As for the structure of the therapeutic apparatus is determined by different medical units and substance along the path is liver tissue mainly, depending more on the clinical situation, we only discuss about the electronic energy value here [40]. When selecting electronic energy value, if there is no vulnerable normal tissue behind the target area, 95% or 90% percentage depth dose can be used to cover the back edge of the target area, so as to ensure that the target area is treated adequately and uniformly. Otherwise, the percentage depth of the back edge of the target area should be set at 80% or 85% to protect the normal tissue behind. For prophylactic radiation on liver in our hypothesis, this is a situation that tumor cells from pancreas have not formed new tumor lesions yet. To consider both safety and effectiveness together, we suggest 80% or 85% is a better choice. Some textbooks suggest [43] that if the percentage depth is set at 85%, the electron energy can be approximately selected as E = 3(MeV/cm)*d (cm). As for the depth of marginal liver metastasis ≤1 cm, E = 3 MeV is suitable in theory.

Thus, we hypothesize that prophylactic intraoperative 3 MeV electron therapy on the surface of liver may prevent postoperative liver metastasis of pancreatic cancer.

Conclusion

In this paper, we present a hypothesis stepwise that intraoperative electron radiation on the surface of liver may prevent postoperative liver metastasis of pancreatic cancer. In the first place, tumor cells shedding from pancreatic cancer localize in the marginal liver preferentially. In the second place, the dose distribution of electron radiation is consistent with the marginal distribution of liver metastasis
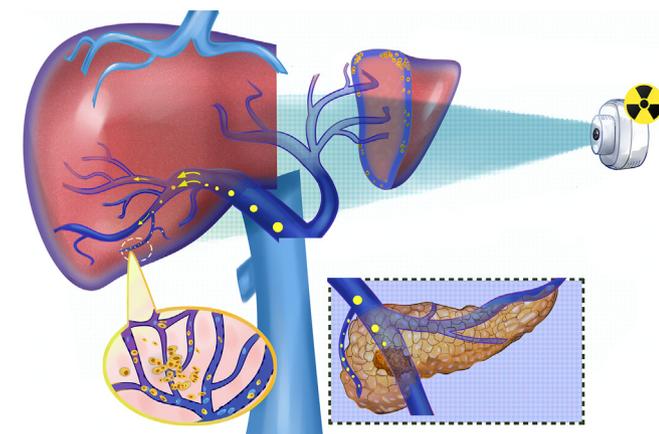
from pancreatic cancer. Theoretically, prophylactic intraoperative 3 MeV electron radiation therapy on the surface of liver may prevent postoperative liver metastasis of pancreatic cancer.

Intraoperative radiotherapy on liver has a particular advantage that it is relatively easy to control radiation dose and treatment area under direct vision, combining the characteristics of marginal liver metastasis and the percentage depth dose of electron radiation fully. In this case, not only can we effectively inhibit the metastasis and growth of cancer cells, but also prevents further deterioration of pancreatic cancer patients' condition. Therefore, this hypothesis has an important clinical significance for postoperative rehabilitation and improvement of patients' survival.

Furthermore, we try to propose an intraoperative electron energy value 3 MeV based on the patients' data of West China hospital in theory, only putting forward a way of thinking. It should be noted that this value is not absolute, but may vary from hospital to hospital and from patient to patient. What's more, when it comes to the dose and mode of clinical treatment, we should take the radiation tolerance of important perihepatic organs, such as stomach and intestine into account to avoid additional damage.

However, as a complicated operation, intraoperative radiotherapy highly demands for superb radiological skills and postoperative nursing observation and intervention. Meanwhile, the adjustment of individualized radiation doses for different patients is also a problem that needs further study. Besides that, intraoperative radiotherapy also has the disadvantage that it causes certain damaging effect on normal liver and surrounding normal tissues, and the responsiveness of circulating pancreatic cancer cells to beta radiation is unknown, so more researches are still necessary.

All in all, in the future, more new ideas for intraoperative preventive radiotherapy are able to be provided by deeply combining the characteristics of radiation and tumor metastasis. Furthermore, extra experimental researches are required, including animal experiment and clinical trials, to further support the safety and effectiveness of this method.

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Conflict of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2019.02.050.

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