

Peer Review File

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Response to Reviewer Comments:

Comment 1: the radiosensitivity is believed to be closely associated with the nature and biological behavior of primary tumor. In this study, patients with liver metastases from different primary cancers were enrolled. The discrepancy of radiosensitivity between different primary tumors was inevitable. Sensitivity analysis is recommended to reveal the effect of the discrepancy on the results.

Reply 1: This is a very important comment, thus we discuss this issue in the discussion section specifically.

Change 1: We added some explanation in discussion section 'Radiosensitivity index (RSI) is believed to be closely associated with the nature and biological behavior of the primary tumor. In this study, patients with liver metastases from different primary cancers were enrolled. Colorectal adenocarcinoma (CRC) was the most common primary tumor type, followed by pancreatic, lung, gastroesophageal, gynecologic, and other tumors. Such composition corresponded to the proportion of primary tumors in most existing studies on RSI (20). A high dose per fraction and a different delivery pattern lowered the duration of SBRT, thereby limiting the potential for sublethal damage repair compared to conventional radiotherapy (CRT). Thus, the RSI of different primary tumors that receive SBRT is different to that of primary tumors that receive CRT. Compared to SBRT, the influence is always smaller than CRT. K.A. Ahmed et al identified a multigene expression index for tumor RSI with validation in multiple cohorts; the median RSI for skin colorectal, stomach, pancreatic, lung, and breast cancer with liver metastases was 0.43, 0.43, 0.42, 0.35, and 0.34, respectively $P=0.0002$ (21). Most primary tumors included in this study displayed no significant difference in RSI. This may due to the distinctive biology of the liver, which is focused on interactions between disseminated tumor cells and the unique resident cell populations of the liver (22). The resident cell populations of the liver (hepatocytes,

liver sinusoidal endothelial cells, Kupffer cells, and hepatic stellate cells) exhibit tumoricidal (apoptosis, phagocytosis, and endocytosis) and/or tumor-promoting activities (extravasation, arrest, colonization, proliferation, angiogenesis, and immunosuppression) in the hepatic metastatic microenvironment. Activities are mediated via soluble signaling factors, direct receptor-mediated cell–cell or cell–ECM contacts, and proteolytic enzymes. This mechanism may cause the hemodynamic features and a unique microenvironment of the liver more important than the location of the primary tumor. Moreover, all primary cancers in this study had received radical treatments, such as resection and radio-chemotherapy, further justifying our focus on liver metastasis.’ (see Page 12-13, line 227-255)

Comment 2: patients with distant metastases were general recognized to be at advanced stage of cancer. Systematic therapy is recommended for these patients with priority. However, more than half patients in the study didn’t receive prior treatment before SBRT or sequential therapy after SBRT. Could you show us the reason and the details.

Reply 2: After review the characteristics of each patients, we found that 43 patients received systematic therapy (prior or sequential therapy), 7 of them only received prior therapy, 18 of them only received sequential therapy, and 18 of them received both. Among the remaining patients, one was unable to tolerate chemotherapy due to basic heart disease, while another one had renal insufficiency. 5 patients couldn’t tolerate chemotherapy because of severe myelosuppression after initial systematic therapy. 7 patients were too old to tolerate systemic treatment. Although there are still some targeted or immune drugs to choose from, they had to give up for economic reasons. And 7 patients only had 1-2 liver metastases, considering the primary tumor was stable, they choose a close follow-up.

Change 2: We added some data in result section ‘22 patients did not receive subsequent systematic therapy due to chemotherapy intolerance, financial reasons, or a shortage of effective treatment at that time.’ (see Page 9, line 157)

Comment 3: the status of primary tumor also affect the outcome of patients. Were the

primary cancer radically resected? Or the metastases were synchronous metastasis. Please display the details in this article.

Reply 3: To answer this comment, we review the characteristics of primary tumor. Among the 65 patients, 62 patients received radical resection when primary tumor was first found. One patient with NPC and two patients with esophageal cancer received radical chemo-radiotherapy. And all of the primary cancers were stable when liver metastasis was occurred.

Change 3: We added some data in result ‘All of the the primary cancers had received radical treatments, such as resection and radio-chemotherapy. And they were stable while liver metastasis was occurring.’ (see Page 8, line 154)

comment 4: colorectal cancer belongs to gastrointestinal cancer. Which cancer does gastrointestinal cancer comprise in line 109? It may confuse the readers that both colorectal cancer and gastrointestinal cancer were listed as primary tumor type.

Reply 4: Thank you for your reminder. This is a misunderstanding caused by language problems. In this article, gastrointestinal cancer means cancer of stomach and esophagus.

Change 4: We change the word ‘gastrointestinal(GI)’ into ‘gastroesophageal’ (see page 8, line 152) , and the same word in table (see page 21, line 369, table 1),(see page 23, line 376, table 3)