Locoregional Chemoradiation for a Patient with BRCA1 Stage IV Pancreatic Adenocarcinoma

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Abstract

Although the highest lifetime cancer risk in the setting of a BRCA 1 mutation is the development of a breast and ovarian malignancy, there is also a < 5% lifetime risk of pancreatic cancer.[1] Recent recommendations suggest annual contrast-enhanced pancreatic MR imaging or endoscopic ultrasound for pancreatic cancer screening for these patients.[2] In this case report, a patient undergoing MRI breast surveillance was incidentally found to have metastatic pancreatic cancer in the liver. The patient was treated with leucovorin, 5-fluorouracil, irinotecan, and oxaliplatin (FOLFIRINOX) alone and was rendered disease-free. Five years later, she developed an isolated nodal recurrence for which she received systemic gemcitabine and cisplatin chemotherapy with a partial response followed by consolidation chemoradiation to 50.4 Gy with intensity-modulated radiation therapy and concurrent capecitabine, with a complete response. This case highlights the potential for long disease-free intervals in the setting of BRCA1-metastatic pancreatic cancer and suggests an individualized role for locoregional radiation.

Keywords: BRCA1, ATM, pancreatic adenocarcinoma

Case Summary

A 70-year-old White woman with no personal history of radiation therapy, but with a prior history of breast cancer following postbilateral mastectomy with transverse rectus abdominis muscle (TRAM) reconstructions, presented for her annual MRI in 2015. She was a heavy smoker with additional oncological history of stage III ovarian cancer 22 years prior and a family history of breast/colon cancer. Multiple bilobar liver lesions were incidentally found on breast MRI and confirmed on triple-phase computed tomography (CT) and positron emission tomography (PET) scans, which also identified a hypermetabolic mass in the body of the pancreas with CA 19-9 > 400. Ultrasound-guided fine-needle aspiration (FNA) of a liver lesion confirmed the diagnosis of T2N0M1, stage IV pancreatic adenocarcinoma. She received 16 cycles of FOLFIRINOX (5-FU at 1800 gm, oxaliplatin at 65 mg/m2, and irinotecan at 100 mg/m2 every 3 weeks) followed by no evidence of disease until 2021, when FNA confirmed a celiac nodal recurrence. Germline testing confirmed BRCA1 and ATM mutations. Chemotherapy with gemcitabine and cisplatin achieved a partial radiographic response. Capecitabine chemoradiation with 50.4 Gy of intensity-modulated radiation therapy (IMRT) achieved a complete response. She did not experience any known early or late toxicity related to her radiation treatment.

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Disclosure/informed consent: Matthew Adams is a member of the *Applied Radiation Oncology* (ARO) Future Content Medical Student Committee. Dr. Hoffe is an editorial board member for ARO and faculty advisor for ARO's medical student committees. Dr. Frakes is a co-head of ARO's gastrointestinal section. No other authors have conflicts of interest to disclose. None of the authors received outside funding for the production of this original manuscript and no part of this article has been previously published elsewhere. The patient has provided informed consent for the publication of this case report.

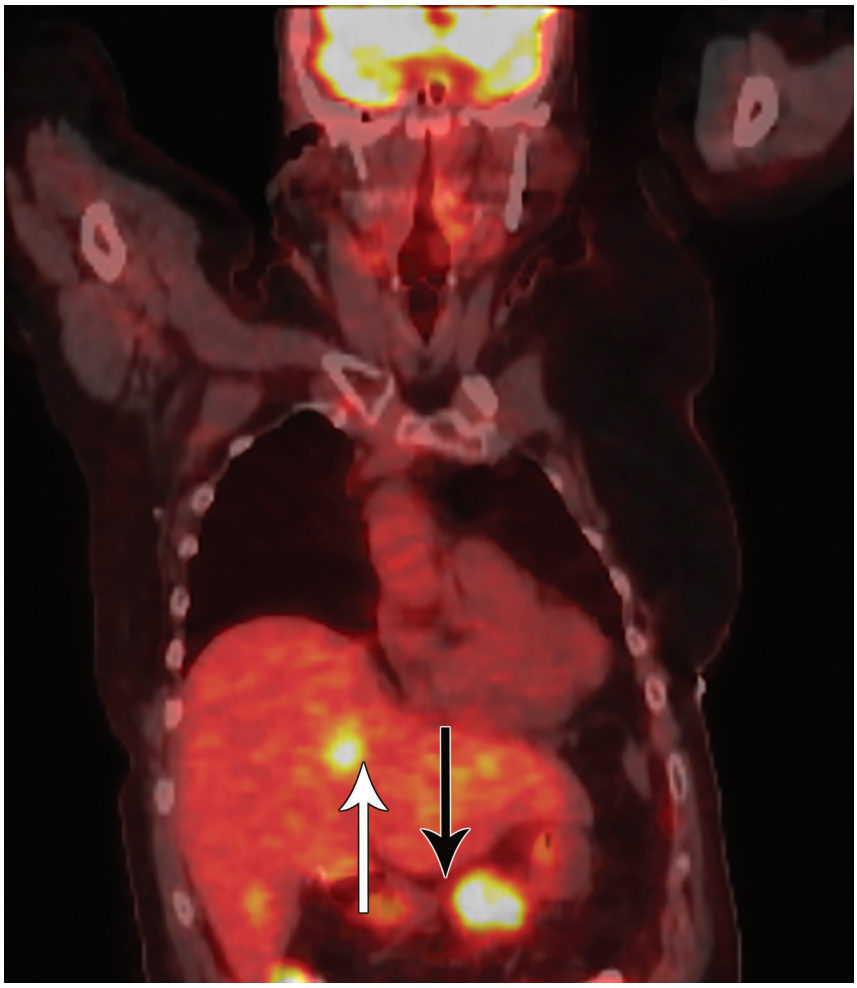


Figure 1. Positron emission tomography / computed tomography (PET/CT) image shows hypermetabolic lesions in the liver and pancreatic body. White arrow shows liver lesion; black arrow points to the pancreas primary tumor.

Diagnosis

In this patient's case, the workup confirmed she had developed a pancreatic body primary adenocarcinoma (**Figure 1**), which metastasized to multiple sites in the liver (**Figure 2**). There were no obvious involved abdominal lymph nodes on imaging at the time of initial diagnosis in 2015. The FNA of one of the liver lesions showed the cells were positive for *CK7*, *CK19*, *CA125*, *CA19-9,* pancytokeratin (*AE1/AE3 CAM5.2*), beta catenin, and *GATA3*.

At the time of recurrence (**Figure 3)** in 2021, FNA of the celiac node was interpreted as poorly differentiated carcinoma consistent with the history of prior pancreatic cancer. After systemic chemotherapy with 3 months of gemcitabine and cisplatin every 21 days, the patient received chemoradiation with capecitabine and an IMRT plan to a dose of 45 Gy in 25 fractions to the clinical target volume followed by a boost of 5.4 Gy in 3 fractions (**Figure 4**) to the gross disease.

Discussion

Despite recent advances in cancer therapy, pancreatic cancer continues to have one of the lowest 5-year overall survival rates (11%).[3] The majority of cases are sporadic but genomic evidence now suggests there is a heterogeneous landscape of molecular subtypes.[4] Several genetic syndromes are associated with pancreatic cancer including mutations in DNA mismatch repair (Lynch syndrome), BRCA1 and BRCA2.[5] The *BRCA* tumor suppressor genes are responsible for numerous functions regarding DNA-damage-dependent cellular checkpoints, DNA repair, and cell death.[6] Mutations that alter the functions of these proteins may lead to targetable treatment. Given the rarity of BRCA-mutated pancreatic cancer (BMPC), it is unclear how much the prognosis differs from wildtype. However, there is agreement regarding the improved sensitivity of BMPC to platinum-based chemotherapies and poly (ADP-ribose) polymerase inhibitors, such as olaparib.[7] The role of radiation therapy in BMPC is not clear, with some laboratory studies showing enhanced radiosensitivity, but clinical studies failing to show clearly improved outcomes.[8]

In addition to BRCA1, our patient had an ATM mutation, which is

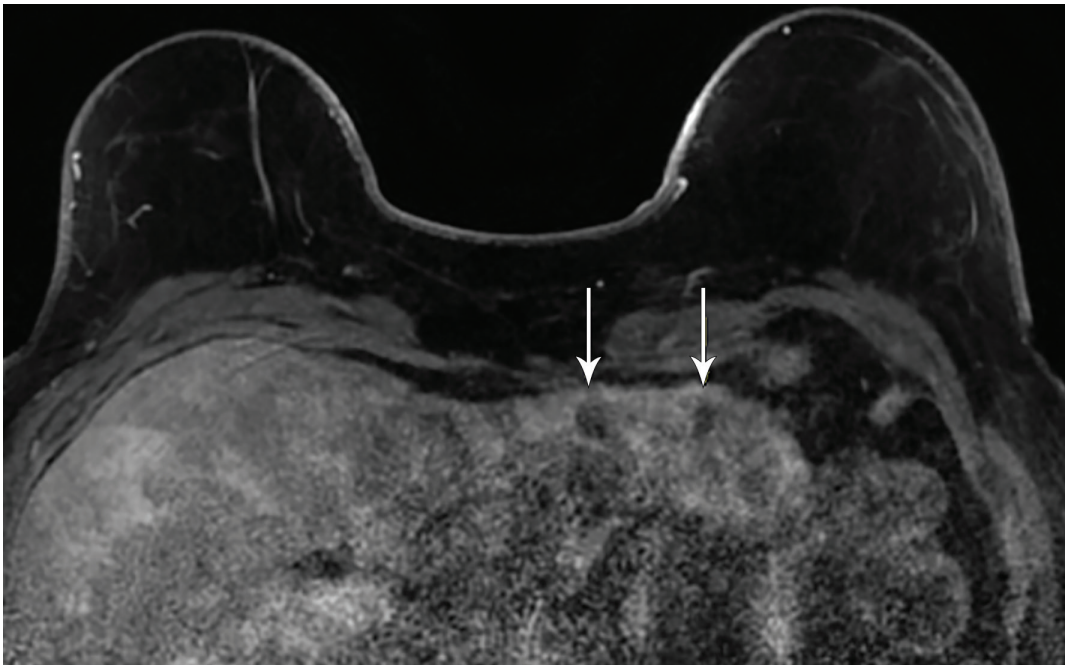


Figure 2. A surveillance MRI scan of the breast shows occult liver lesions (white arrows).

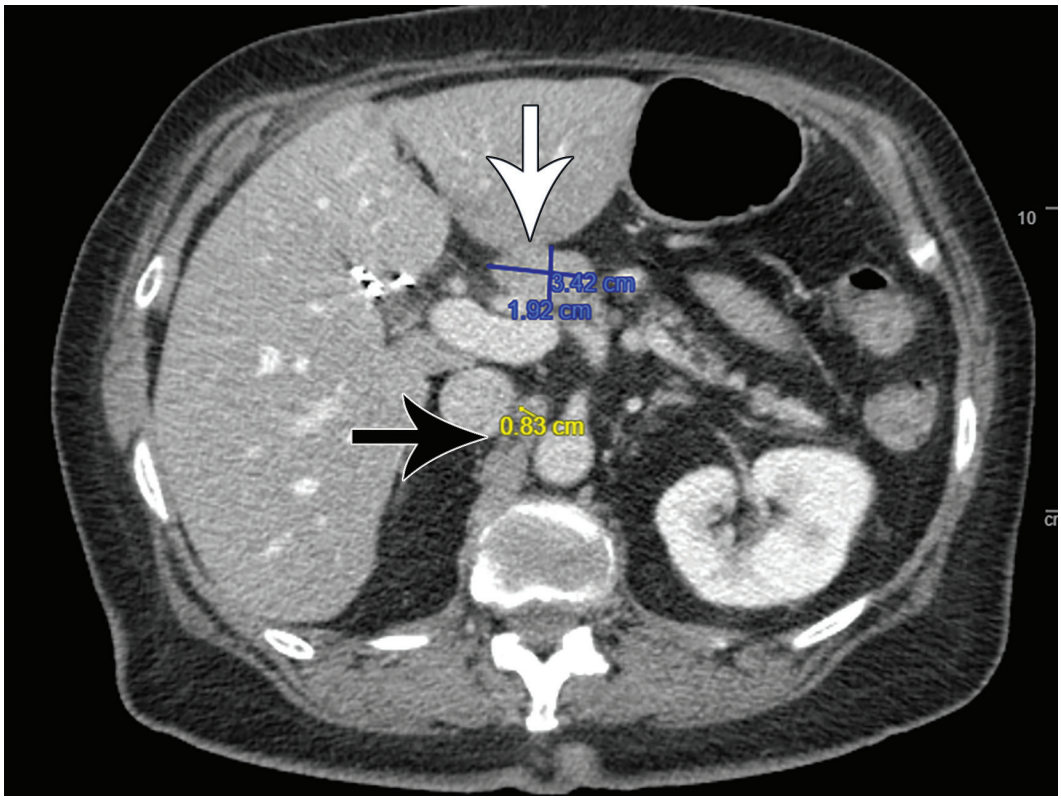
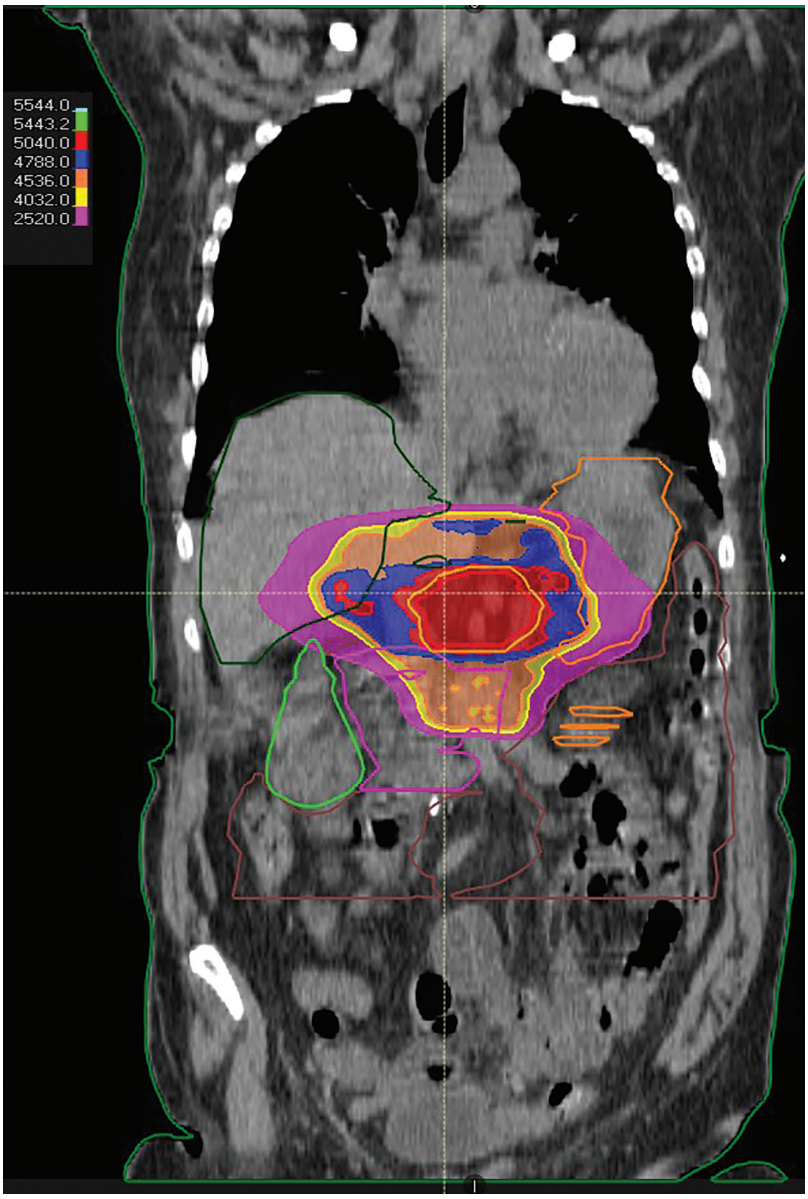


Figure 3. Axial contrast-enhanced scan showing nodal recurrence in the celiac and aortocaval regions. Celiac nodes shown at the white arrow; aortocaval node shown at the black arrow.

associated with ataxia telangiectasia and has been characterized by extreme radiosensitivity.[9] Recent studies have shown that both heterozygous and homozygous ATM inactivation are associated with increased radiosensitivity[10] and that patients with cancer and both BRCA and ATM mutations may have significantly increased radiosensitivity and an enhanced response to radiation therapies.[11] ATM mutations have been of concern due to the potential of excessive radiation-associated toxicity particularly in breast cancer. Recent evidence indicates, however, that overall there is no excess in clinically significant acute toxicity, although caution is warranted as subvariants such as c5557G>A may have a higher risk of late toxicity

Figure 4. Axial contrast-enhanced scan showing nodal recurrence in the celiac and aortocaval regions. Coronal dose distribution of the composite plan: 45 Gy in 25 fractions to the clinical target volume, followed by 5.4 Gy in 3 fractions to the gross tumor volume, for a total dose of 50.4 Gy with intensity-modulated radiation therapy.



or radiation-induced contralateral breast cancer.[12,13]

The clinical implications of germline genetic mutations illustrate the importance for genetic testing of all patients diagnosed with pancreatic cancer. Our patient declined *BRCA* testing after her first breast cancer diagnosis in her 30s, believing it was no longer important since she underwent bilateral mastectomy, only to be diagnosed with ovarian and pancreatic cancer over the next 40 years. Early genetic testing would have also revealed her ATM H231fs mutation earlier, which is significant given the associated increased cancer predisposition to malignancies of the lung, thyroid, pancreas and other areas, which could have led to more frequent screening intervals. In addition, the ATM mutation has relevance to her sensitivity to platinum chemotherapy agents since this mutation can be associated with increased response rates.[14] The current standard of care is to offer genetic testing to all patients diagnosed with pancreatic cancer.[15]

In our case, the patient had a clinical complete response of her pancreatic primary and metastatic liver disease to FOLFIRINOX. Our patient has vastly exceeded the average prognosis of her condition with over 6 years of survival to date and 5 years of remission prior to recurrence.[16] Interestingly, our patient relapsed in the celiac and adjacent nodes only without any recurrence in the pancreas primary site or liver. This was confirmed with an MRI scan of the abdomen before treatment initiation. After 3 months of gemcitabine and cisplatin chemotherapy, the MRI showed a persistent nodal viable tumor. Since multidisciplinary tumor board evaluation centered around her current age of 76 and her comorbidities, focusing on treatments to maintain her quality of life were preferred, leading to the decision to proceed with consolidation to all sites of nodal activity with chemoradiation (CRT).

For gastrointestinal tumor sites with adenocarcinoma histology, there is a paucity of literature supporting radiation therapy for stage IV disease. In metastatic cancers of the esophagus, there is a potential survival benefit associated with CRT, suggesting that patients with chemotherapy intervals of 3 months or longer have improved outcomes, approaching 20% at 5 years for gastroesophageal junction tumors.[17] In colorectal cancer patients, after immune checkpoint blockade, oligoprogression can be a frequent pattern of failure and local therapy strategies that include radiation may improve clinical outcomes.[18] In pancreatic cancer, there is as yet no literature to support the role of consolidation to nodal targets post-chemotherapy for stage IV disease.

For our patient, the decision to offer her consolidation CRT was made

after extrapolation from esophageal adenocarcinoma outcomes, recognizing that her radiosensitivity was likely increased secondary to her underlying BRCA1 and ATM mutational status. IMRT was incorporated to maximize her normal tissue sparing since the potential to enhance organ at risk (OAR) sensitization was unknown. The patient tolerated her CRT well and did not have any high-grade toxicities. At nearly 1 year post-therapy, her CA 19-9 and imaging have not shown evidence of recurrence. The multidisciplinary tumor board has discussed the possibility of olaparib as maintenance therapy. Due to the results of the recent POLO trial,[19] the patient prefers to consider this if she recurs and not as maintenance therapy, given the lack of a survival benefit.

Conclusion

This case highlights the potential for long disease-free survival in BRCA-mutated metastatic pancreatic cancer. Although enhanced radiosensitivity of BRCA-mutated tumors has been described in the laboratory, correlative clinical outcomes are lacking. The resolution of primary and metastatic disease on systemic FOLFIRINOX therapy for 5 years postdiagnosis supports the efficacy of platinum-based chemotherapy in this patient population. After regional nodal recurrence, salvage CRT was delivered to the abdomen, and nearly 1 year post-treatment, the patient remains radiographically and biochemically without evidence of disease. As expert consensus opinions recommend all patients with pancreatic cancer obtain genetic testing, more patients may be identified with BMPC, and a personalized strategy that includes radiation may be warranted for patients that respond to systemic therapy.

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