

The Role of Fiducial Placement in the Treatment of Pancreatic Cancer: The Expanding Role of Endoscopic Ultrasound

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Pancreatic adenocarcinoma is the second most common gastrointestinal malignancy and the fourth leading cause of cancer mortality in the United States [1]. Both local and systemic therapies are integral in the treatment of pancreatic cancer. Aggressive local treatment leads to improved local control which can translate into improved overall survival [2]. For patients with locally advanced pancreatic cancer, chemoradiation provides improvement in survival when compared with chemotherapy alone [3,4]. The chemotherapy may be administered together or sequentially with the radiation therapy. In radiotherapy for pancreatic cancer, adequate dose delivery to target tissue is hampered by the radiosensitivity of healthy adjacent organs. Several studies have demonstrated that aggressive local therapy with radiation dose escalation can improve local control. Radiation dose escalation has been attempted through the use of intraoperative radiotherapy, stereotactic body radiotherapy, and intensity-modulated radiotherapy (IMRT) [5-7]. IMRT is a recent advancement in the delivery of radiotherapy, facilitating improved radiation dose delivery to the tumor [8]. IMRT delivers high-precision radiotherapy using a computer-controlled linear accelerator to deliver precise radiation doses to specific areas. The presence of the small bowel within the "lymphatic volume" limits traditional radiotherapy to maximal doses of 50 Gy (5000 rads). The use of IMRT enables delivery of doses as high as 54 Gy (5400 rads) to the tumor. This permits the ability to escalate radiation doses to the tumor while maintaining or reducing healthy tissue exposure. This advancement in radiation technique improves the chance of secondary resection, improves local control for unresectable disease, and reduces symptoms related to local progression.

Image-guided radiotherapy (IGRT) is a recent technique that allows the delivery of precisely aimed radiation beams to tumors [9]. IGRT ensures that IMRT is delivered with optimal accuracy. IGRT utilizes advanced imaging technology to verify target position before and during radiotherapy. Prior methods to target culprit pancreatic lesions with bone landmarks have proven to be unreliable. IGRT is dependent on reference points by which the target lesion can be identified and tracked, particularly in cases such as pancreatic tumors where the target lesion is subjected to movement during respiration. IGRT relies on fiducial markers to target and track the location of the tumor in real time. This ensures that radiation treatment is delivered to the tumor with pinpoint accuracy with decreased damage to the normal surrounding tissues.

Fiducials are inert radiologic markers that are implanted into the target lesion for both localizing and tracking. The minimum of 1 to 2 fiducials are required. Fiducials are placed either within the target malignant culprit lesion or within 1 cm of a smaller target lesion. Traditionally, fiducials are placed either intraoperatively or percutaneously (by ultrasonography or computed tomography guidance) [10]. While percutaneous approaches for fiducial placement are ideal for superficial lesions, they tend to be less feasible for deep pancreatic lesions. Recently, fiducial markers have been successfully placed endoscopically. Since the introduction of Endoscopic Ultrasound (EUS)-guided fine needle aspiration in 1992, numerous

novel EUS-based interventions and techniques have emerged. EUS-guided placement of fiducial markers before targeted radiation therapy is a novel clinical application of therapeutic linear EUS [11]. EUS-guided fiducial placement provides potential advantages over the surgical or percutaneous methods. EUS minimizes complications by offering a minimally invasive approach with real-time visualization and Doppler imaging capability. Furthermore, EUS allows access to deeper structures within the gastrointestinal tract periphery. Although this technique is relatively new, its role in the management of gastrointestinal malignancies is expanding.

Fiducials can be delivered with 19-gauge or 22-gauge needles [12,13]. Standard fiducials are cylindrical gold seeds, measuring 3 to 5 mm in length and 0.8 to 1.2 mm in diameter. Sterile bone wax can be used to hold and separate preloaded gold fiducials within the 19-gauge needle. The new smaller, longer fiducial markers are 10 mm in length and 0.35 mm in diameter. It comes preloaded on a needle carrier delivery device for use with 22-gauge needle which allow for optimal placement [12].

Several studies have subsequently described the feasibility and safety of this approach with technical success rates of 85% to 100% with a low complication rate [12-17]. Reported complications include cholangitis, acute pancreatitis, minor bleeding, fever, abdominal pain, and elevated liver enzymes [12,13,15,16]. Some have suggested prophylactic antibiotics as a way to avoid some of these reported complications [17]. Although fiducials can spontaneously migrate from the initial implantation site, the rate of migration is relatively low (7%) and no migration-related complications have been reported [13]. The newer fiducials are a flexible gold coiled design, which may reduce the incidence of fiducial migration. Failure to place a fiducial in the target location often was due to anatomic factors, including surgically altered anatomy or limitations of equipment [13]. Placement of fiducial using 22-gauge needle may permit greater access compared with the 19-gauge needle technique [17]. The greater flexibility of the 22-gauge needle permits easy passage of the needle through the endoscope despite the acute endoscope angulation or torquing commonly encountered when targeting lesions in the pancreatic head. Furthermore, the 22-gauge needle does not produce the same endoscope rigidity when compared to the 19-gauge needle,

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minimizing the limitations in echoendoscope manipulation or tip deflection [12]. As the therapeutic applications of EUS continue to expand, better accessories are required to meet treatment needs. It is important to consider the development of flexible, multishot needles which are able to deploy multiple fiducials in one pass. Finally, making fiducials in unique shapes would facilitate their distinction from operative staples.

Chemoradiation therapy for pancreatic cancer can improve survival and facilitate palliation of obstructive symptoms and cancer related pain. Additionally, chemoradiation can contribute to tumor downstaging, and allow patients with locally advanced disease to undergo potentially curative surgical resection. Intensity-modulated radiotherapy with image-guided technology has become the preferred modality to deliver increased doses of radiation to the tumor while minimizing damage to the surrounding healthy tissue. Fiducials implanted into the target lesion allow for real time adjustments of the radiation beam to compensate for body and respiratory movements. EUS-guided deployment of fiducials carries significant advantages over intraoperative or percutaneous placement. The development of dedicated single-pass, multiple fiducial, EUS-guided deployment devices will further enhance the procedure feasibility and expand our therapeutic options for therapy of unresectable pancreatic cancer.

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