Upfront Chemotherapy Followed by SBRT in Pancreatic Cancer

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Multimodality therapy involving stereotactic body radiation therapy (SBRT) is safe and feasible in older patients with localized pancreatic cancer. Surgical resection was associated with improved clinical outcomes. As such, older patients who complete chemotherapy should not be excluded from aggressive local therapy when possible.

stereotactic body radiation therapy SBRT older patients

1. Introduction

Pancreatic cancer is the third leading cause of cancer-related deaths in the United States, responsible for over 48,000 deaths each year [1]. In fact, it is projected to become the second most common cause of cancer-related deaths by the year 2040 [2]. Treatment of localized disease usually involves a combination of chemotherapy, radiation therapy, and surgical resection [3]. Unfortunately, even with aggressive therapy, outcomes are guarded with a five-year overall survival (OS) rate of less than 15% for borderline resectable and locally advanced pancreatic cancer (BRPC/LAPC) [4].

Pancreatic cancer can be considered a disease of older patients with the median age of diagnosis of 70 years [5]. In fact, two thirds of newly diagnosed patients are over 65 years [5]. As the population continues to age, the incidence of pancreatic cancer in the older patients is expected to increase [6]. However, optimal management of this group of patients is largely unknown given that clinical trials consist predominantly of younger patients, and as such, the results cannot necessarily be applied to the treatment of older patients [7][8]. Furthermore, only a small proportion of older patients currently receive what would be considered standard of care therapy for non-older patients [9][10][11][12]. In fact, one study demonstrated that only 44% of patients over 65 years with LAPC received any treatment at all [13]. As such, more information is needed regarding the optimal management of older patients with pancreatic cancer.

Older patients are more likely to have co-morbidities or poor performance status that precludes aggressive therapy such as surgical resection and adjuvant therapy [9]. Stereotactic body radiation therapy (SBRT), which is used for the purpose of margin sterilization in the neoadjuvant setting or for improved local progression-free survival (LPFS) in the definitive/unresectable setting, may have a role in these patients. There have been only a handful of studies investigating the role of SBRT in older patients [14][15][16][17][18]. Unfortunately, many of these studies are limited by heterogeneous treatment and disease characteristics.

2. Current Discussion

In older patients who complete chemotherapy, aggressive local treatment with SBRT and surgery is well tolerated, with just three events (5.3%) of late grade 3 radiation toxicity and two events (5.3%) of Clavien-Dindo grade 3b toxicity in those who underwent resection. Researchers also show that surgical resection is associated with improved clinical outcomes such as OS, DMFS and PFS, including an impressive median OS of 29.1 months.

Older patients with pancreatic cancer represent a challenging population given the aggressive nature of the disease and because many will not be candidates for multimodality therapy due to co-morbidities and poor performance status. As such, older patients (≥70 years) are underrepresented in clinical trials, accounting for 46% of the United States cancer population, but compromising only 20% of trial participants [7][8]. As such, the optimal management for these patients is unknown. Furthermore, many older patients do not receive standard of care treatment. Studies have shown that older patients are less likely to undergo surgical resection and receive adjuvant chemotherapy [19][20][21]. In addition, a study by Krzyzanwoska et al. of LAPC, demonstrated that only 44% of older patients received any form of treatment [13]. Therefore, additional studies are warranted to determine the most appropriate management for this group of patients.

Several studies have demonstrated the feasibility of SBRT in older patients and are shown in **Table 1** [14][15][16][17][18]. Three studies, including the current study, included older patients who underwent surgery. While cross-study comparisons are limited and the cohort was likely more fit given that all patients completed chemotherapy, the fact that a large proportion (67%) underwent surgical resection is noteworthy and higher than other studies (34%, 10%) [16][18]. This likely led to the higher median OS in the patients (19.6 versus 14.0 and 10–13 months) [16][18]. Conversely, the median OS was < 10 months in the studies, which included only inoperable patients [14][15][17]. In the current report, patients who underwent resection had improved median OS (29.1 vs. 7.0 months, $p = 0.005$). Sutera et al. demonstrated similar results (28.3 vs. 11.4 months, $p = 0.002$) [18]. Interestingly, the disease extent was similar in the study (BRPC: 47.4%, LAPC: 52.6%) to that of Sutera et al. (resectable/BRPC: 46.2%, LAPC: 53.8%) and Zhu et al. (BRPC: 32.5%, LAPC: 67.5%). The difference in resection rate can likely be attributed to institution-specific surgical practice patterns. For example, at the institution, all BRPC/LAPC are taken for surgical exploration as long as they have stable disease, no medical contraindications, and if there is a reasonable pathway for resection. Additionally, the cohort was likely more fit given that researchers selected for patients who completed chemotherapy. Of the 19 patients who did not undergo resection in the cohort, only two had medical contraindications/advanced age. Of the 38 patients who underwent resection, 22 (57.9%) and 2 (5.3%) experienced Clavien-Dindo grades < 3a and 3b toxicity, respectively, which is consistent with rates from other series, which included patients of all ages [22][23]. These findings suggest that surgery can be well tolerated in older in patients who complete chemotherapy and should not be withheld solely based on age criteria, as resection may significantly improve outcomes in these patients.

Table 1. Literature on SBRT for older patients.

Reference	Relevant Patients	Median Age (Years)	Median SBRT Dose/Fractions	Surgical Resection	Acute Radiation ≥ G3 Toxicity	Late Radiation ≥ G3 Toxicity	Median Survival after SBRT (Months)
Kim et al. (2013) [14]	24	86	24 Gy/1 fraction	No	1 (4%)	0 (0%)	7.6
Yechieli et al. (2017) [15]	20	83	35 Gy/5 fractions	No	1 (10%)	2 (10%)	6.4
Zhu et al. (2017) [16]	323	73	30–46.8 Gy/5–8 fractions	Yes (10%)	2 (0.5%)	0 (0%)	10.0–13.0
Ryan et al. (2017) [17]	29	74	28 Gy/5 fractions	No	2 (7%)	1 (3%)	8.0
Sutera et al. (2018) [18]	145	79	36 Gy/3 fractions	Yes (34%)	1 (1%)	3 (2%)	14.0
Current Study	57	74	33 Gy/5 fractions	Yes (67%)	0 (0%)	3 (5%)	19.6

e patients may be at risk of uncontrolled tumor growth, which can cause significant local morbidity such as cholangitis, biliary obstruction, GI bleeding, and celiac plexopathy, which in turn, can drive both morbidity and mortality [24]. In fact, the median OS for untreated pancreatic cancer is just 2.5 months [25]. Therefore, minimally invasive treatments, such as SBRT, are important for this group of patients. Several studies have investigated the role of SBRT in inoperable older patients, with encouraging results [14][15][17]. Kim et al. reported on 26 patients with a median age of 86 years, who were treated with SBRT + chemotherapy [14]. They reported a median OS of 7.6 months and 1-year LPFS rate of 41.2%, with no late grade > 3 toxicity. Of note, there was a 70% rate of symptom relief after SBRT. Ryan et al. reported on 29 patients with inoperable disease treated with SBRT + chemotherapy [17]. They reported a median OS of 8.0 months and 1-year LPFS of 78%, with a symptom relief rate of 58%. There was only one episode of late grade 3 toxicity. In the current study, 19 patients underwent SBRT alone, with a median OS of 7.0 months and one-year LPFS of 72.0%. There were no late grade > 3 radiation toxicity events. Interestingly, the one-year LPFS rate reported by Kim et al. is significantly lower, despite utilizing a higher median biologically effective dose. One explanation is that a lower percentage (48%) of patients received chemotherapy when compared to the study by Ryan et al. (83%) and the study (100%), highlighting the role of systemic therapy in local control. Taken together, these findings demonstrate that SBRT for older patients with medically inoperable/unresectable disease is safe, feasible, and can provide adequate symptom relief.

One area of active investigation, which may be relevant to older patients, is dose escalation for inoperable pancreatic cancer. Retrospective data has shown that increased radiation dose can improve both OS and LPFS [26][27][28][29]. Studies, including the current one, demonstrate that SBRT to conventional doses is safe and feasible, but that outcomes can be suboptimal especially in older patients who cannot undergo surgical resection or receive systemic therapy [14][15][16][17][18]. Therefore, dose-escalated therapy may be of benefit in these patients. However, very little is known about the safety of increased radiation dose in older patients. Additionally, the prolonged

treatment time associated with dose escalation must weighed against the limited life expectancy and potential detriment to quality of life in these patients. As such, further studies investigating the safety and efficacy of dose escalation in this older population is warranted.

There are some limitations of the current study, including its retrospective design. Patients received various chemotherapy regimens, which may have impacted clinical outcomes, although this was controlled for during statistical analysis. current study population was also likely more fit when compared to others, because researchers only included patients who completed chemotherapy, limiting cross-study comparisons. Moreover, it also would have been useful to demonstrate underutilization of local therapies in elderly patients as compared to other age groups, certainly a worthwhile subject of future study, but this was not possible with current institutional data. Furthermore, some patients had follow-up locally at outside institutions, likely leading to underreporting of treatment-related toxicity. researchers were also unable to comment on symptom palliation as this information was not available for review. The strengths of this study include its relatively large sample size, homogenous treatment characteristics with regards to general treatment paradigm and SBRT dose/fractionation, and long follow-up time. Despite the study's limitations, the findings add relevant information to the role of SBRT in the treatment of older patients.

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