Original Article

Partial splenic embolization to alleviate thrombocytopenia in stage III and IV pancreatic ductal adenocarcinoma patients

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Background: Thrombocytopenia may be a concern in treating pancreatic ductal adenocarcinomas (PDAC). Due to anatomic position these tumors commonly cause narrowing or occlusion of the splenic vein which may lead to hypersplenism and thrombocytopenia due to sequestration. PDAC patients with thrombocytopenia have limited options for treatment. Partial splenic embolization (PSE) is a procedure developed as an alternative to splenectomy in individuals with hypersplenism. The purpose of our study was to review outcomes of PSE on thrombocytopenia in stage III and IV PDAC patients.

Methods: From November 2015 through January 2018, we conducted a retrospective chart analysis of 8 patients with stage III or stage IV pancreatic cancer who had undergone PSE. The primary objective of this retrospective study was to understand the utility of PSE in treating thrombocytopenia in pancreatic cancer patients by the effect on the individual's platelet count and the subsequent exposure to chemotherapy treatment. Specific demographic data points were recorded including date of diagnosis, stage, location of primary origin, and site of metastasis. Other data including hospital days post-embolization, post-embolization syndrome (PES), days to return of chemotherapy, survival, and pre/post platelet counts at designated intervals were reviewed.

Results: Seven-eighths patients were diagnosed with stage IV pancreatic adenocarcinoma with the pancreatic head being the most common primary site (50%). Most common site of metastasis was liver. PES was found in 5/8 patients with the average number of hospital days after the procedure 1.38 (SD =1.06). Mean platelet count pre-splenic embolization was 93.00 (SD =12.59). One-week post-embolization mean platelet count was 147.00 (SD =69.60). Four-week ($\overline{\chi}$=183.60, SD =64.93), six-week ($\overline{\chi}$=148.40, SD =40.58), and three-month ($\overline{\chi}$=161.00, SD =79.07) intervals were used to further assess platelet change. The results of the ANOVA were significant, $F(4)$ =3.65, P=0.027, η_p^2 =0.48. Post-hoc analyses revealed significant differences between one-week and four-week post-embolization (P=0.008). Time to restarting chemotherapy ranged from 1 to 129 days with an average day to restarting chemotherapy of 24.12 (SD =42.70). The median overall survival was 7.22 months.

Conclusions: In considering our study's small sample size, PSE should be considered a safe approach in managing thrombocytopenia long-term in stage III or stage IV PDAC patients. PSE may allow for further chemotherapy to improve overall survival.

Keywords: Partial splenic embolization (PSE); thrombocytopenia; pancreatic cancer

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Introduction

In 2019, it is estimated that there will be 56,770 new cases of pancreas cancer and an estimated 45,750 people will die of this disease, making it the fourth leading cause of cancer related deaths in the United States (1). From 2007–2013 there was a 5-year survival rate of 8.5% in patients with pancreatic cancer (1). Pancreatic ductal adenocarcinomas (PDAC) represent the most common (85%) type of pancreatic neoplasm and metastasis is usually found on presentation (2). Furthermore, primary pancreatic tumors tend to extend into adjacent structures such as the duodenum, the portal vein, or superior mesenteric vessels (2). This local extension to adjacent structures eventually leads to narrowing of major vessels resulting in portal hypertension and thus hypersplenism. The concept of hypersplenism has been studied in liver disease and thought to be a result of portal hypertension causing pooling and sequestration of all corpuscular elements of the blood, predominantly thrombocytes (3).

Partial splenic embolization (PSE), first performed by Spigos *et al.* in 1979 (4), entails embolization of a portion of the splenic parenchyma utilizing distal embolic agents such as Gelfoam and polyvinyl alcohol particles. PSE has been demonstrated to be a safer and less invasive alternative in comparison to splenectomy and is considered the first-line therapy for thrombocytopenia secondary to hypersplenism in many institutions (5-8). PSE has been used to safely palliate the effects of hypersplenism by reducing the volume of splenic parenchyma using conventional transarterial embolization techniques (9-13). By addressing the effects of hypersplenism, this results in improving platelet counts and thereby allows the continuation of chemotherapy in cancer patients. For example, Kauffman *et al.* concluded PSE for cancer patients with thrombocytopenia can be performed safely and effectively to increase platelet counts and should be considered an option to facilitate the initiation or resumption of systemic chemotherapy (SC) (14). Another study by Luz *et al.* concluded that thrombocytopenia from hypersplenism as a result of SC, can be alleviated by PSE thereby allowing the continuation of SC (15).

To date, there have been no studies that have reviewed the impact of PSE on thrombocytopenia in advanced PDAC patients. We conducted a retrospective study examining the impact of PSE on thrombocytopenia in individuals with stage III and IV PDAC.

Methods

We conducted a retrospective chart analysis of patients with stage III or stage IV pancreatic cancer who had undergone PSE between July 5, 2017 and June 4, 2018. Charts were reviewed after approval from HonorHealth Institutional Review Board (IRB). De-identified data including date of diagnosis, cancer stage, location of primary, site of metastasis and date of PSE was collected. Other data extrapolated from patient's charts included the length of stay in hospital days, platelet counts, symptoms of post-embolization syndrome documented, time in days to resume cancer treatment and which agent administered, and survival information. We also determined maximum coronal diameter of spleen, splenic volume (by utilizing Aquarius iNtuition vers. 4.4 software), and splenic vein patency from pre-embolization cross sectional imaging. The embolic agent used for PSE was recorded. Patient platelet counts were obtained pre-PSE platelet and at one week, one month, and three months.

PSE technique

PSEs were performed by four experienced interventional radiologists using standard techniques. All procedures were distal embolizations with selection of embolic agent at the discretion of the radiologist. Agents used were size calibrated non-resorbable microspheres (Embospheres, Merit Medical, South Jordan, UT, USA) measuring 300–500 microns (5 cases), 500–700 microns (4 cases), and one case using Gelfoam slurry. Angiographic technique in all cases was to advance a microcatheter into distal splenic artery branches (to the degree feasible based on anatomy) and perform embolization preferentially targeted for the lower pole of the spleen when possible. The embolization endpoint was roughly 30% devascularization of splenic parenchyma. As shown in *Figure 1*. It was found that cone beam CT was very helpful intra-procedurally to qualitatively assess the volume of spleen embolized. Patients were admitted for at least overnight observation and pain control. Patients were not given prophylactic vaccinations post-procedure.

Results

Eight patients were identified with either Stage III or IV PDAC and who had undergone PSE. As seen in *Table 1*, seven of the eight patients were diagnosed with stage IV pancreatic adenocarcinoma with the pancreatic head being the most common primary site (50%). Most common site of metastasis was liver (seven of eight). The median age was 55 years old (range, 39–72 years old). Post-embolization

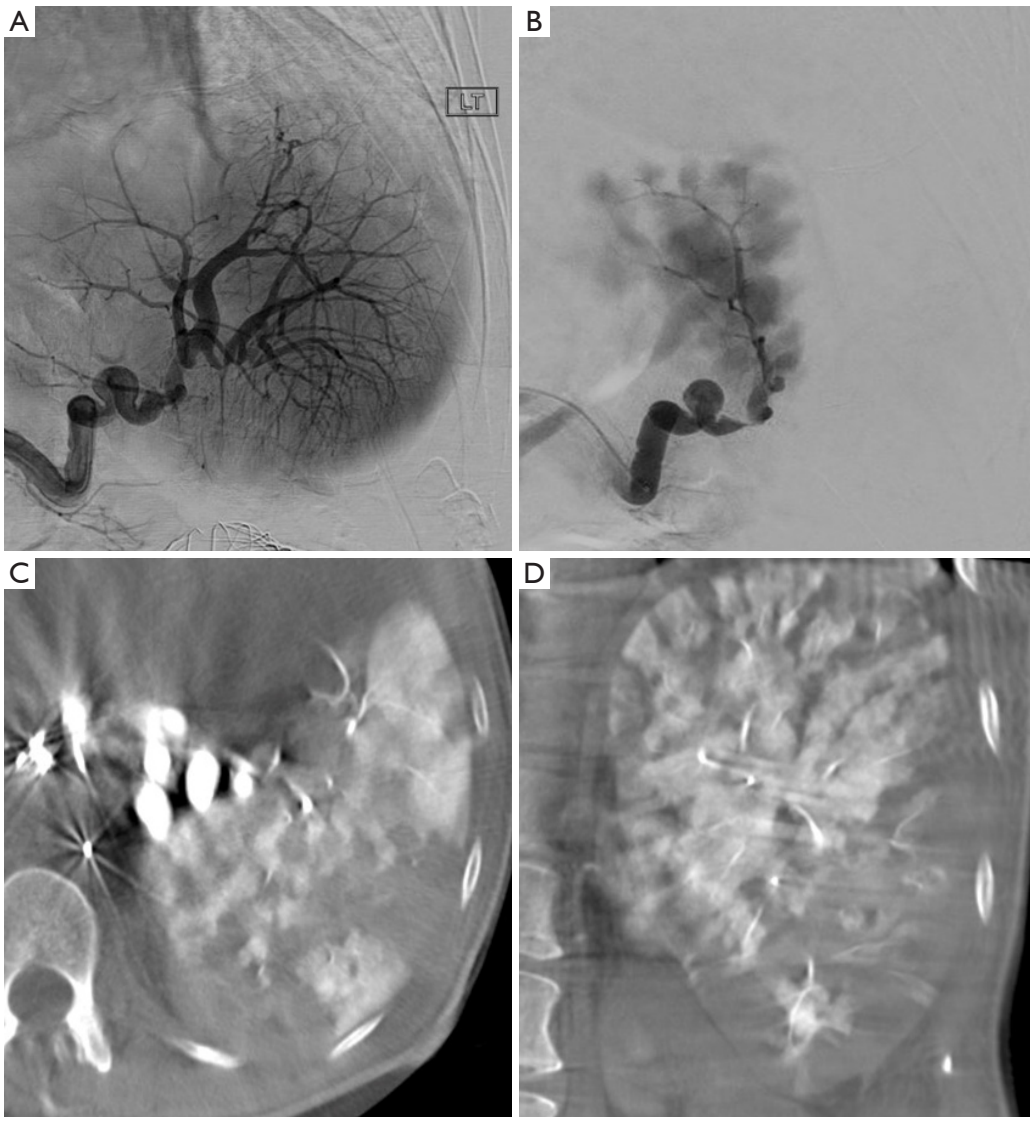

Figure 1 Pre and post embolization digital subtraction angiograms. (A) Pre-embolization DSA of spleen showing uniform enhancement throughout spleen; (B) post-embolization DSA of spleen showing devascularization of lower pole splenic parenchyma and patchy devascularization elsewhere. Enhancing areas maintain arterial flow; (C) axial cone beam CT image of a different patient post-embolization. Cone beam CT allows for obtaining conventional CT-like images in the interventional suite and gives more precise visualization of devascularized parenchyma; (D) coronal reconstruction of cone beam CT post-embolization. In coronal plane the desired preferential devascularization at the lower pole is well demonstrated. These images tend to be more useful than conventional DSA in estimating the percent of spleen devascularized. DSA, digital subtraction angiogram.

syndrome (PES) was found in five of eight patients with the average number of hospital days after the procedure 1.38 (SD =1.06). The average days to restarting chemotherapy was 24.12 (SD =42.70) and all eight individuals were able to proceed to therapy. As seen in *Table 1*, most patients resumed FOLFIRINOX, except for one that continued on maintenance metformin. Median overall survival after splenic embolization was 7.22 months (range, 4.67–20.83 months).

Table 2 lists the platelet counts prior to PSE, then at weeks 1, 4, 6, and 12. Mean platelet count pre-splenic embolization was 93.00 (SD =12.59). One-week post-embolization mean platelet count was 147.00 (SD =69.60),

Table 1 Patient demographics of individuals with advanced pancreatic cancer undergoing partial splenic embolization

Patient #	Cancer stage	Location of primary	Site of metastasis	# Hospital days	Post-embolization syndrome	Time to post-embolization txt (days)	Post-embolization txt	Alive/dead	Overall survival post SPE (months)
1	IV	Tail	Liver	1	Yes (fever)	1	Metformin	Alive	10.23
2	IV	Body	Lung, liver	1	Yes (fever, LLQ abd pain)	11	Gemcitabine, clinical trial	Deceased	4.67
3	III	Head/ductal	None	1	Yes (LUQ abd pain)	129	5FU	Alive	8.03
4	IV	Head	Liver	1	No	8	FOLFOX	Deceased	5.23
5	IV	Head & Body	Liver	1	No	12	Clinical trial, maintenance therapy	Deceased	7.67
6	IV	Head	Liver	1	Yes (fever, abd pain)	8	FOLFIRINOX	Alive	6.77
7	IV	Tail	Stomach, spleen, liver and peritoneum	1	No	5	FOLFIRINOX	Deceased	20.83
8	IV	Neck/Body	Liver, supraclavicular LN	4	Yes (LUQ abd pain)	19	Clinical trial	Alive	4.77

txt, treatment; PSE, partial splenc embolization; LN, lymph node; abd, abdomen; LLQ, left lower quadrant; LUQ, left upper quadrant.

four-week was 183.60 (SD =64.93), six-week was 148.40 (SD =40.58), and three-month was 161.00 (SD =79.07). The results of the analysis of variance (ANOVA) were significant, $F(4)=3.65$, P=0.027, $\eta_p^2=0.48$. Post-hoc analyses revealed significant differences between one-week and four-week post-embolization (P=0.008). *Figure 2* provides an overview of the estimated marginal means of platelet counts over the three-month study period.

Discussion

We performed a retrospective review of eight patients with advanced PDAC. As shown by previous studies, PSE can be considered an accepted and effective alternative to splenectomy for the management of hypersplenism from various pathologies including malignancy directly involving the spleen (9,10,13,16-18). All eight patients in the current study had clinical evidence suggestive of hypersplenism from PDAC. With respect to radiological evidence of hypersplenism, 7/8 met the basic radiologic criterion for splenomegaly (length of spleen greater than 12 cm). A time consuming but more accurate calculation of splenic size is total volume, with 314.5 cm^3 having been proposed as the upper limit of normal (19). By this volume definition all 8/8 study patients exhibited splenomegaly (range, 473–886 cm^3). Importantly, all patients also had imaging evidence of splenic vein stenosis or occlusion, presumed to cause venous outflow obstruction and congestive hypersplenism. The laboratory evidence included significant thrombocytopenia potentially limiting the administration of SC. Our mean number of days to return to SC for the patients was found to be 24. All, but three of the patients in the study had an elevation in their platelet count within 1 week after undergoing PSE. We also found a statistical significance in elevation of platelet counts between one-week and four-weeks post-embolization (P=0.008).

Metastatic PDAC typically has a median survival of between 11.1 months with FOLFIRINOX, 8.5 months with nab-paclitaxel plus gemcitabine, and 6.8 months with gemcitabine monotherapy (20,21). We found a median overall survival of 7.22 months among our 8 patients with advanced PDAC several of whom had already underwent prior therapeutic regimens. The longest survival was found to be 20.83 months.

With respect to duration of the procedure, we recorded fluoroscopy time and sedation time in our reports. For fluoroscopy time the mean was 19.3 min (range, 8.7–69.4 min), for sedation time the mean was 84 min

Table 2 Platelet counts at designated time intervals

Patient #	Pre procedure platelet count	1 week plt count	4 week Plt count	6 week Plt count	12 week Plt count
1	86	84	135	126	104
2	75	170	206	146	251
3	67	95	–	99	91
4	97	85	115	162	77
5	107	252	280	208	238
6	67	140	83	154	–
7	136	117	–	–	248
8	100	144	182	100	135

Weeks 4, 6, 12 are +/– 1 week. plt, platelet.

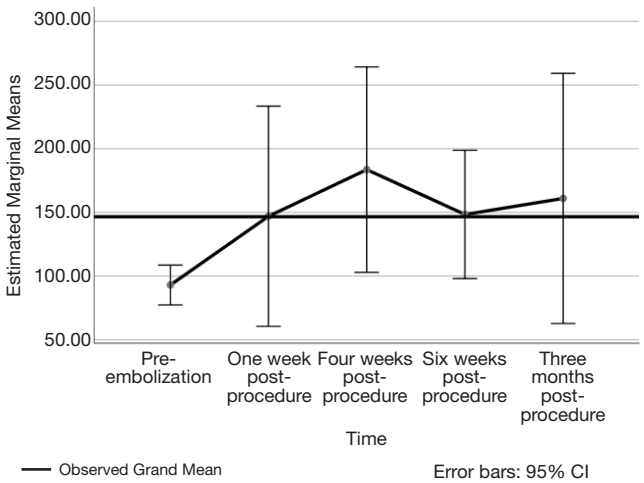

Figure 2 Estimated marginal means of platelet counts over the study period.

(range, 55–167 min). This duration can be compared to that of a laparoscopic splenectomy (145.1 min) and open splenectomy (77.3 min) not including sedation time (22). Sedation time is defined in IR as time from first sedation drug administration to time when radiologist leaves the room. We didn't routinely record sedation time until a couple of years ago so that data is lacking for the first two procedures for one of our patients.

Despite the benefits of PSE, it can come with potential complications including PES. Potential complications of PSE include intermittent fever, abdominal pain, nausea, vomiting, splenic abscess, splenic rupture, pneumonia, refractory ascites, pleural effusions, gastrointestinal bleeding and PES (8,11,23,24). PES is defined by low-grade fever, mild abdominal pain, nausea and traditionally treated supportively (5,7,14,25,26). Rarely, severe complications from PSE can arise including sepsis, portal vein thrombosis, and pulmonary infections (24,27). After the retrospective chart analysis, 5/8 or 62.5% of the studied sample met the criteria of PES with the most prominent symptoms of fevers and left sided abdominal pain. In addition to 62.5% of the patient population meeting criteria for PES, one patient (#7 during procedure 11/13/15) experienced a minor complication. There was a small dissection of distal splenic artery due to guide wire manipulation with no detrimental clinical consequence. Although with any procedure, PSE contains its own potential complication including PES, we did not appreciate any major or severe complications in our patient population. There were no other identifiable major or severe complications in our study group.

As seen in *Figure 1*, we used a rough procedural endpoint of about 30% splenic infarction based on personal experience to balance effectiveness and risk. Furthermore, due to our small sample size, it was difficult to determine if one type of embolic material be superior to others. The embolic agent was selected based on preference of experienced interventional radiologist performing the procedure. We believe total distal splenic embolization using particles could lead to unacceptable post-procedural pain and perhaps increase risk of abscess formation.

Limitations of the study include retrospective analysis and small sample size. Even though our study size consisted of eight patients, they were all diagnosed with hypersplenism from PDAC. Other studies reported that utilized PSE examined a variety of malignancies with very few cases of PDAC (14,15). For example, Kauffman *et al.* found median overall survival of 9.40 months (95% confidence interval, 8.2–10.7 months) and mean peak platelet value of 293 K/uL

among the 28 patients studied (14). The malignancies of their patient population ranged from hepatocellular carcinoma to periampullary/duodenal carcinoma (14). These results were similar is way of substantially increasing platelets values, but differed in there was a longer overall survival rate (9.4 months) compared to our findings (7.22 months).

Despite the small sample size, we were still able to show statistical significant data especially in improving/alleviating thrombocytopenia at 6 and 12 weeks post PSE. Not only did our study demonstrate a statistical significant increase in our platelet counts at the six-week and three-month intervals thereby allowing continuation of SC, we found an overall median survival of 7.22 months. In conclusion, PSE can be considered an effective and tolerable method to alleviate thrombocytopenia in stage III and IV PDAC patients.

PSE should be considered another therapeutic option to alleviate thrombocytopenia secondary to hypersplenism. Validation of its use is warranted in prospective clinical trials.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/apc.2019.05.01). E Borazanci: Speaker's Bureau from Ipsen; Advisory Honoraria from Ipsen, Corcept, Fujifilm; Research funding from Institutional funding with Bristol-Myers Squibb, Pharmacyclics, Idera, Daiichi Sankyo, Minneamrita Therapeutics, Ambry Genetics, Mabvax, Eli Lilly, Samumed. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This report was approved by the Institutional Review Board of HonorHealth medical center (No. 1123527-2). Informed consent was waived due to the retrospective nature of the study.

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