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Quality of life assessment for patients undergoing irreversible electroporation (IRE) for treatment of locally advanced pancreatic cancer (LAPC)

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ABSTRACT

Background: IRE is a non-thermal ablative modality that has been shown to be safe and efficacious in LAPC and liver tumors, but few studies have shown its effects on patients' (QOL). The goal of this study is to evaluate quality-of-life (QOL) before and after irreversible electroporation (IRE) therapy for treatment of locally advanced pancreatic carcinoma (LAPC).

Methods: Between 11/2014 and 12/2016, patients scheduled for IRE therapy for LAPC were offered QOL questionnaires (EORTC QLQ-C30 V2.0) before surgery and 1,3 and 6-months after surgery. Descriptive statistics, one-way ANOVA and effect-size calculations were used in analysis of the 15 modules.

Results: Eight-four prospective patients were enrolled with a median age of 59.08 years (range 27.38 −75.72) all who completed 6 months QOL surveys. Global health status scale showed lower average score at 3 and 6 months($p = 0.001$). Symptoms scales constipation and insomnia showed higher averages at 3 months ($p = 0.007$ and $p = 0.003$ respectively), while dyspnea had higher average at 6 months ($p < 0.001$). Finally, changes were noted with worse diarrhea symptoms scale at 1 and 3 months ($p < 0.001$). Otherwise all QOL side effects were normalized at 3 months after IRE.

Conclusions: The preponderance of symptoms at 3–6 months, symptom profile, and the use of additional therapy on majority of patients suggests other interrelated clinical factors influenced results (e.g. chemotherapy toxicity). This demonstrates that IRE therapy does not adversely affect QOL in the short term in patients with LAPC.

Introduction

Pancreatic cancer is known to have a poor prognosis, with one and five-year survival rates of 28% and less than 5% respectively.[1,2] It is considered the 4th leading cause of cancer-related death in the United states and has an incidence rate of 8/100,000 globally, with at least 40% of all new pancreatic cancers being diagnosed as Stage 3, locally advanced pancreatic cancer (LAPC).[1]

Typically, patients with locally advanced unresectable pancreatic cancer have tumor invasion into adjacent critical structures, particularly the celiac and superior mesenteric arteries. Pancreatic tumors become symptomatic at a very advanced stage; therefore, a small percentage (15–20%) of patients may undergo therapeutic local consolidative resection/therapy. In the remaining patients, there might be either advanced locoregional disease without distant metastases (expected survival of 6–12 months) or locoregional disease with distant metastases (expected survival of 3–6 months).[3]

Irreversible electroporation (IRE) is a technology that is based on the irreversible increase of permeability of the cellular membrane with the use of high voltage (3000 V), short pulse (70–90 us) electric currents. IRE is one of the latest technological advances, and recent studies have been performed on its application in the local treatment of pancreatic cancer. Improvements in intra-operative imaging, electrodes, and ultrasound (US) have enabled the technology to accurately treat tumors.[4–6] IRE has been applied to patients not considered suitable for surgical resection (IRE in-situ) and in conjunction with surgical resection (IRE with margin accentuation) who have received or will be receiving CRT.[7,8] Thus it aims to offer consolidative disease control, with symptom relief, control of pain, and definitive eradication of the lesion.[9]

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IRE is unique from other surgical devices on the market because it is a non-ablative based therapy. This technology utilizes high electrical energy pulses delivered to a pre-defined tissue volume as determined by multiple probes to induce apoptosis.[10] Based on biological principles, the electrical energy pulses cause shifts in transmembrane potentials, inducing shifts in the lipid bilayer such that nanopore formation occurs.[10] When nanopore formation occurs, there is disruption in cellular homeostasis, which is typically temporary. If the transmembrane potential difference is large enough (i.e., the electrical energy pulse is large enough), these nanopores will become permanent. When this occurs the cell can no longer maintain homeostasis and initiates an apoptotic signaling cascade, ultimately leading to cell death and tissue necrosis.[10,11]

This technology has been utilized to cancer in multiple organs, including liver, lung, kidney, breast, prostate and pancreas.[10] The vast majority of literature has shown IRE to be both safe and efficacious for the disease treated.[7,12,13] Few studies, however, have examined the beneficial effect/quality of life (QOL) of patients who undergo IRE. Some studies utilizing this technology to treat prostate cancer have shown positive results, but very few have examined IRE in treatment of locally advanced pancreatic cancer.[14,15] The goal of this study was to evaluate the QOL via questionnaires provided before and after treatment of patients undergoing IRE and assess if a statistically significant beneficial difference was present among the questionnaire categories. We hypothesize that patients will report no detrimental effects to QOL (defined by symptom severity and functional status assessment) after IRE treatment.

Methods

Patient selection & study design

The study obtained Institutional Review Board Approval. All patients received informed consent. All patients 18 years or older were considered for study and were enrolled in this prospective QOL study. Only patients diagnosed with locally advanced pancreatic cancer (Stage III) and receiving IRE therapy for treatment were considered for study.[16] Briefly, there must be no distant lymph node involvement and there must be tumor-vessel involvement with the following conditions: 1) Abutment, impingement or encasement of the superior mesenteric vessels 2) abutment or short encasement of the hepatic artery and 3) no involvement with the celiac artery.[16] Patients determined by an experienced surgical oncologist with advanced knowledge in gastrointestinal oncology and in consultation with a radiologist to have Stae III unresectable pancreatic adenocarcinoma were considered for the study. The optimal patient selection, the use of induction chemotherapy and the precise IRE technique for stage III – In-situ IRE has been described previously.[17–19]

Questionnaires

Eligible patients were offered quality of life questionnaires (QLQ). This study utilized the European Organization for Research and Treatment Center (EORTC) Quality of Life Questionnaire C30 version 2.0 (EORTC QLQ-C30 V2.0) and the Edmonton Symptom Assessment Profile (ESAS). Briefly, the EORTC questionnaire contained 30 total items subdivided into 15 modules that assessed various aspects of patient QOL including symptom severity, functional assessment, financial difficulties, and global health status over the past week. The ESAS is a similar questionnaire that asks patients to assess nine symptoms common in cancer patients; the severity is based at the time of the assessment. The literature has shown the EORTC to be a reliable multidimensional self-report instrument.[20] The ESAS has also been validated.[21] Questionnaires were provided before surgery and 1, 3, and 6 months afterwards. The QOL surveys were completed either in person or over the phone at the 3 or 6 month visit if the patient could not return to Louisville for follow up. Scoring and analysis followed guidelines stated in the EORTC QLQ-C30 scoring manual provided by the EORTC.[22,23]

Statistical analysis

Descriptive statistics were used to analyze demographics and values were reported as either mean with standard deviation or median with range. To test for IRE surgical therapy effects on patient QOL the data from patients was aggregated per each of the 15 modules and a one-way repeated ANOVA was used to determine differences between pre- and post-operative QOL. ESAS data was analyzed using the same method. Results were further interrogated using a Bonferroni post-hoc test to examine pre-operative QOL to 1, 3 and 6 months post-operative QOL. The null-hypothesis was there is no difference between the pre-operative group and each of the post-operative groups. Significance level was set to $\alpha = 0.05$. Statistical significance was further interrogated via effect size (ES) calculations in order to highlight more clinically relevant changes.[24,25] The effect size is another way of quantifying the differences between time points in this study (https://www.leeds.ac.uk/educol/documents/00002182.htm). For the purposes of this study effect sizes were categorized as small ($ES \leq 0.2$ or 50% change from prior time point), small to moderate ($0.2 < ES \leq 0.5$, 60–70% change from prior time point), moderate to large ($0.5 < ES < 0.8$, 70%–80% change from prior time point), and large ($ES \geq 0.8$, greater than 80% change). Statistical software package V23.0 was used to perform analyses.

Results

Patient characteristics

From November 2012 to December 2015, 84 patients (38 male, 46 female) were found to have LAPC and treated by IRE. The median age was 59 (range of 27–76). Approximately 92.8% of patients enrolled in study were Caucasian. The body mass index (BMI) was 24.09 ± 3.78. Hypertension and smoking was found to be the most common past medical history reported with diabetes as the 2nd most common; 28 patients reported significant cardio-pulmonary histories. Finally, all patients underwent some form of additional chemotherapy (Table 1). All 84 patients completed there interval QOL surveys.

Quality of life

All patient reported data was analyzed after 6 month QOL survey completions. A one-way repeated measured ANOVA was conducted to compare the effect of IRE treatment on the aforementioned 15 quality of life categories for the EORTC questionnaire at 1, 3 and 6 months post-operatively. Statistical comparisons between post-operative time points were reported for completeness, but were not considered in interpretations. Analysis revealed a statistically significant difference among the following 8 categories: (1) Constipation (Wilks' lambda = 0.73, $F(3,39) = 4.71$, $p = 0.007$); (2) Diarrhea (Wilks' lambda = 0.41, $F(3,39) = 18.50$, $p < 0.0001$); (3) Pain (Wilks' lambda = 0.68, $F(3,39) = 6.12$, $p = 0.002$); (4) Dyspnea (Wilks' lambda = 0.54, $F(3,39) = 11.22$, $P < 0.0001$); (5) Insomnia (Wilks' lambda = 0.70, $F(3,39) = 5.49$, $P = 0.003$); (6) Financial Difficulties (Wilks' lambda = 0.50, $F(3,39) = 13.16$, $p < 0.001$); (7) Physical Functioning (Wilks' lambda = 0.71, $F(3,39) = 5.27$, $P = 0.004$); (8) Global Health Status

Table 1
Demographic data for patients provided EORTC QLQ-C30 questionnaires pre and 1,3,6 post-operative time points. SD = standard deviation.

Patient Characteristics	
Median age (range)	59.08 (27.38–75.72)
Gender	
Male (%)	38(45.2)
Female (%)	46(54.8)
BMI (avg ± SD)	24.09 ± 3.78
Race	
White	78
African American	4
other	2
Past medical History	
Cardiac	8
Vascular	10
Pulmonary	11
Diabetes	17
Hypertension	21
Smoking	36
Alcohol	13
Adjuvant Therapy	84
Xeloda	28
Gemzar	26
Gemzar and Xeloda	22
FOLFIRINOX	8
Hospital Stay (avg ± SD)	5.6 ± 3.43

(Wilks' lambda = 0.64, F (3,39) = 7.23, P = 0.001) (Tables 2 and 3). The remaining 7 categories showed no statistical significance: (1) Fatigue (Wilks' lambda = 0.94, F (3,39) = 0.82, p = 0.49); (2) Nausea & Vomiting (Wilks' lambda = 0.95, F (3,39) = 0.75, p = 0.53); (3) Appetite Loss (Wilks' lambda = 0.96, F (3,39) = 0.56, p = 0.64); (4) Role Functioning (Wilks' lambda = 0.91, F (3,39) = 1.24, p = 0.31); (5) Emotional Functioning (Wilks' lambda = 0.90, F (3,39) = 1.48, p = 0.23); (6) Cognitive Functioning (Wilks' lambda = 0.95, F (3,39) = 0.66, p = 0.58); (7) Social Functioning (Wilks' lambda = 0.82, F (3, 39) = 2.79, p = 0.053) (Tables 2 and 3).

Due to the 8 significant categories, post-hoc Bonferroni tests were performed and reported on these categories. Both Pain (Table 2) and Physical Functioning (Table 3) scales showed significance between post-treatment months (p = 0.002 at 3–6 months, p = 0.003 at 1 month–6 month, peaking at the 3-month interval and coinciding with the initiation of additional chemotherapy, which was started between 6 and 8 weeks post IRE. This is confirmed by the lack of adverse QOL effects at 1-month post IRE in these symptoms. The Global Health Status (GHS, Table 3) showed lower averages (improvement in global health) at 3 and 6 months (p = 0.02 and p = 0.001) respectively, while the Diarrhea scale was worse at 3 months, and then improved at 6-month follow up (p = 0.04 and p < 0.001 respectively) (Table 2). The other (Table 3) scales showed only significant differences at a single month. Symptom scales Constipation and Insomnia (Table 2) had higher averages at 3 months' post-treatment (Pre IRE to 3 month, p = 0.01

Table 2
Symptom severity and financial difficulty scales analyzed via one-way repeated measure ANOVA. Bonferoni Post-Hoc test used to analyze relationship between pre-operative and 1,3, and 6 post-op time points. Comparison between post-operative time points reported for completion. $\alpha = 0.05$.

ANOVA Results (Symptom scales)									
Scales	Time Points	Mean	ANOVA P-Value	Post-Test Significance (Bonferoni)					
				PreIRE-1	PreIRE-3	PreIRE-6	1–3	3–6	1–6
Constipation	PreIRE	11.11	**0.007**[a]	0.07	**0.01**[a]	0.01	1.00	1.00	1.00
	1 month	29.37							
	3 month	36.51							
	6 month	27.38							
Diarrhea	PreIRE	15.08	**<0.001**[a]	**0.04**[a]	**<0.001**[a]	1.00	**0.001**[a]	**<0.001**[a]	0.20
	1 month	27.78							
	3 month	47.22							
	6 month	17.06							
Fatigue	PreIRE	34.26	0.49	1.00	1.00	0.753	1.00	1.00	1.00
	1 month	34.66							
	3 month	35.05							
	6 month	42.06							
Nausea & Vomiting	PreIRE	12.30	0.53	1.00	1.00	1.00	1.00	1.00	0.989
	1 month	10.32							
	3 month	11.71							
	6 month	15.48							
Pain	PreIRE	18.25	**0.002**[a]	1.00	0.10	0.35	0.10	**0.001**[a]	0.20
	1 month	18.65							
	3 month	30.16							
	6 month	10.32							
Dyspnea	PreIRE	3.97	**<0.001**[a]	0.15	0.13	**<0.001**[a]	1.00	**0.04**[a]	**0.03**[a]
	1 month	10.71							
	3 month	11.90							
	6 month	8.18							
Insomnia	PreIRE	19.05	**0.003**[a]	0.13	**0.006**[a]	0.14	1.00	1.00	1.00
	1 month	32.14							
	3 month	39.15							
	6 month	22.28							
Appetite Loss	PreIRE	22.76	0.64	1.00	1.00	1.00	1.00	1.00	1.00
	1 month	24.80							
	3 month	21.14							
	6 month	19.10							
Financial Difficulties	PreIRE	28.57	**<0.001**[a]	1.00	0.15	**0.002**[a]	**0.02**[a]	**<0.001**[a]	**0.05**[a]
	1 month	26.19							
	3 month	44.05							
	6 month	9.92							

[a] The higher the score the worse the QOL symptom.

Table 3
Functional assessment and global health status scales for EORTC QLQ-C30 questionnaire. Results analyzed via one-way repeated measure ANOVA with Bonferoni post-hoc test, $\alpha = 0.05$.

ANOVA Results (Functional & Global Health Status Scales)									
Scales	Time Points	Mean	ANOVA P-Value	Post-Test Significance (Bonferoni)					
				PreIRE-1	PreIRE-3	PreIRE-6	1–3	3–6	1–6
Physical Functioning	PreIRE	89.27	**0.004**[a]	0.48	1.00	1.00	0.5	0.17	**0.003**[a]
	1 month	82.52							
	3 month	87.82							
	6 month	92.62							
Role Functioning	PreIRE	76.98	0.31	1.00	1.00	0.36	1.00	1.00	1.00
	1 month	73.21							
	3 month	73.41							
	6 month	65.67							
Emotional Functioning	PreIRE	82.74	0.233	1.00	1.00	1.00	1.00	0.46	0.29
	1 month	79.93							
	3 month	79.23							
	6 month	86.44							
Cognitive Functioning	PreIRE	86.11	0.58	1.00	1.00	1.00	1.00	1.00	1.00
	1 month	86.71							
	3 month	90.87							
	6 month	89.48							
Social Functioning	PreIRE	78.18	0.05	0.10	0.44	0.46	1.00	1.00	1.00
	1 month	65.08							
	3 month	69.84							
	6 month	68.65							
Global Health Status	PreIRE	72.62	**0.001**[a]	1.00	**0.02**[a]	**0.001**[a]	0.63	0.18	**0.05**[a]
	1 month	67.86							
	3 month	63.19							
	6 month	51.99							

[a] Higher score better QOL, except for GHS which is reversed (i.e. lower score better QOL).

Table 4
Edmonton Symptoms and Assessment Scale analyzed via one-way ANOVA. Bonferoni Post-Hoc test used to analyze relationship between pre-operative and 1,3, and 6 post-op time points. Comparison between post-operative time points reported for completion. $\alpha = 0.05$.

ANOVA Results (ESAS)									
Scales	Time Points	Mean[a]	ANOVA P-Value	Post-Test Significance (Bonferoni)					
				PreIRE-1	PreIRE-3	PreIRE-6	1–3	3–6	1–6
No Pain	PreIRE	1.94	**0.0004**	1	0.248	1	0.28	**<0.05**	0.42
	1 month	2.06							
	3 month	3.07							
	6 month	1.28							
Not Tired	PreIRE	2.53	**0.005**	0.612	1	0.181	0.30	0.06	**0.003**
	1 month	3.51							
	3 month	2.54							
	6 month	1.51							
Not Nauseated	PreIRE	1.28	**0.02**	1	1	1	1	**0.013**	0.603
	1 month	1.31							
	3 month	1.45							
	6 month	0.70							
Not Depressed	PreIRE	1.69	**0.008**	1	1	0.063	1	**0.008**	0.244
	1 month	1.80							
	3 month	2.07							
	6 month	0.70							
Not Anxious	PreIRE	1.59	**0.006**	1	1	**0.03**	1	**0.011**	0.08
	1 month	1.42							
	3 month	1.73							
	6 month	0.51							
Not Drowsy	PreIRE	1.63	**0.0004**	1	1	0.272	1	**0.012**	**0.05**
	1 month	1.46							
	3 month	2.11							
	6 month	0.64							
Best Appetite	PreIRE	2.50	0.087	1	1	1	0.72	1	0.10
	1 month	3.38							
	3 month	2.44							
	6 month	1.99							
Best feeling of well- being	PreIRE	2.94	**0.001**	1	1	**0.01**	1	**0.003**	**0.01**
	1 month	3.10							
	3 month	3.03							
	6 month	1.37							
No shortness of breath	PreIRE	0.625	**0.032**	0.075	**0.04**	0.35	1	0.46	1
	1 month	1.94							
	3 month	1.65							
	6 month	1.24							

[a] Lower score better QOL.

Table 5
Effect size calculation tables for functional assessment and global health status scales from EORTC QLQ-C30 questionnaire provided to patients undergoing IRE to treat LAPC at pre and 1,3,6 post operative time points. Large effect size (ES ≥ 0.8) bolded.

Effect size (functioning and global health scales)										
Scale	Time point	Mean[a]	SD	Common SD	Difference between means			Effect Size		
					PreIRE-1	PreIRE-3	PreIRE-6	PreIRE-1	PreIRE-3	PreIRE-6
Physical Functioning	PreIRE	89.27	18.71	14.84	6.75	1.46	−3.35	0.45	0.1	0.23
	1 month	82.52	16.36							
	3 month	87.82	13.76							
	6 month	92.62	8.57							
Role Functioning	PreIRE	76.98	31.22	28.60	3.77	3.56	11.31	0.13	0.01	0.40
	1 month	73.21	25.67							
	3 month	73.41	29.17							
	6 month	65.67	28.05							
Emotional Functioning	PreIRE	82.74	15.99	16.93	2.81	3.50	−3.70	0.17	0.21	0.22
	1 month	79.93	18.47							
	3 month	79.23	20.91							
	6 month	86.44	10.63							
Cognitive Functioning	PreIRE	86.11	16.83	15.60	−0.60	−4.76	−3.37	0.04	0.31	0.22
	1 month	86.71	19.04							
	3 month	90.87	15.04							
	6 month	89.48	10.09							
Social Functioning	PreIRE	78.18	23.71	26.37	13.10	8.34	9.53	0.50	0.32	0.36
	1 month	65.08	31.79							
	3 month	69.84	24.96							
	6 month	68.65	24.19							
Global Health Status	PreIRE	72.62	20.85	21.57	4.76	9.43	20.63	0.22	0.44	**0.96**[a]
	1 month	67.86	20.04							
	3 month	63.19	16.77							
	6 month	51.99	27.26							

[a] Higher score better QOL, except for GHS which is reversed (i.e. lower score better QOL).

and p = 0.006 respectively). Finally, the Dyspnea scale showed higher average (p = 0.001) and Financial Difficulties showed lower average at 6 months (p = 0.002) (Table 2).

The ESAS data showed 8 out of 9 categories with a statistically significant difference. Only 3 categories (Not Anxious, Best Feeling of Well-being, No Shortness of Breath) showed a statistically significant difference between pre- and post-operative time points (Table 4), with all 6-month scores demonstrating improvement in all 3 QOL questions. The following categories showed a statistically significant difference: (1) No Pain (Wilks' lambda = 0.534, F (3,29) = 8.42, p = 0.0004); (2) Not Tired (Wilks' lambda = 0.645, F (3,29) = 5.33, p = 0.005); (3) Not Nauseated (Wilks' lambda = 0.717, F (3,29) = 3.815, p = 0.02); (4) Not Depressed (Wilks' lambda = 0.667, F (3,29) = 4.82, p = 0.008); (5) Not Anxious (Wilks' lambda = 0.665, F (3,29) = 5.08, p = 0.006); (6) Not Drowsy (Wilks' lambda = 0.535, F (3,29) = 8.41, p = 0.0004); (7) Best Feeling of Well-being (Wilks' lambda = 0.56, F (3,29) = 7.72, p = 0.001); (8) No Shortness of Breath (Wilks' Lambda = 0.74, F (3,29) = 3.35, p = 0.03) (Table 4). The category Best Appetite (Wilks' lambda = 0.80, F (3,29) = 2.41, p = 0.09) did not show a statistically significant difference (Table 4).

The Post-HOC Bonferroni test was performed in same fashion for the EORTC data and all comparisons are reported. Not Anxious and Best Feeling of Well-being showed a statistically lower average at 6 months' post-operative time points, while the category No Shortness of Breath showed an average higher value at 3 months' post-operative time point (Table 4). The remaining 5 categories showed statistically significant differences for comparison of post-operative time points of 1, 3, and 6 months.

Quality of life (effect size)

To further analyze the statistical difference among time points for each category, extent of these differences (ES) were calculated and reported. There was a large change in 3 distinct categories: (1) Global Health Status, (2) Diarrhea, and (3) Dyspnea (Table 5 and Table 6) from pre-operative, to 1 month and then 3 months. Both of the symptoms scales showed similar effect size changes. For Diarrhea 88% of patients had worsening diarrhea (EF 1.24) at 3 months compared to pre-operative(Table 6). The Global Health Status scale showed an 86% of all patients had better perceived overall health at 6 months (Table 5). While these symptoms showed large effect-size changes, there were multiple scales that showed moderate to large effect-size changes as well. The Constipation scale showed 78% change in the group (ES = 0.76) at 3 months when compared to pre-op.

The ESAS data was analyzed following the same methods as the EORTC data. No large effect size changes were noted in any of the 9 categories (Table 7). Multiple categories showed moderate changes from Pre-IRE. The categories Not Anxious and Best Feeling of Well-being showed some changes at 6 months when compared to Pre-IRE, while the No Pain and Not Tired categories showed moderate changes at 3 and 1 months, respectively (Table 7).

Discussion

The overall objective of this study was to evaluate the QOL of patients undergoing IRE to treat LAPC, and determine if IRE had short-term and/or long-term (6-months) detriment in QOL. The first assessment for the QOLl effects of IRE demonstrated no initial changes at 1 month in either functional assessment or symptom severity, but with variable changes in symptom severity reported at 3 and 6 months, corresponding to baseline. In attempt to correlate with smaller numbers, we did observe that the type of adjuvant chemotherapy obviously may play a role in the QOL of patients post IRE procedures; however since this was not the aim of this study, further subset analysis was not performed. The key goal of this study was to evaluate if IRE in LAPC caused any type of permanent loss of QOL in patients, so that a more informed decision abot the use of IRE could be presented to prospective patients.

Table 6
Effect size calculation table for symptom severity scales from EORTC QLQ-C30 questionnaire provided to patients undergoing IRE to treat LAPC. Large effect size (ES ≥ 0.8) bolded.

Effect size (symptom scale)										
Scale	Time point	Mean	SD	Common SD	Difference between means			Effect Size		
					PreIRE-1	PreIRE-3	PreIRE-6	PreIRE-1	PreIRE-3	PreIRE-6
Constipation	PreIRE	11.11	27.22	33.41	−18.25	−25.40	−16.27	0.55	0.76	0.49
	1 month	29.37	36.41							
	3 month	36.41	46.45							
	6 month	27.38	15.54							
Diarrhea	PreIRE	15.08	24.64	25.76	−12.70	−32.14	−1.99	0.49	**1.24***	0.08
	1 month	27.78	26.20							
	3 month	47.22	25.22							
	6 month	17.06	26.92							
Fatigue	PreIRE	34.26	26.08	26.45	−0.40	−0.80	−7.81	0.02	0.03	0.30
	1 month	34.66	26.11							
	3 month	35.05	22.14							
	6 month	42.06	30.75							
Nausea & Vomiting	PreIRE	12.30	27.56	20.34	1.99	0.60	−3.17	0.10	0.03	0.16
	1 month	10.32	19.37							
	3 month	11.71	16.57							
	6 month	15.48	15.68							
Pain	PreIRE	18.25	17.96	22.48	−0.40	−11.90	7.94	0.02	0.53	0.35
	1 month	18.65	22.53							
	3 month	30.16	27.54							
	6 month	10.32	20.81							
Dyspnea	PreIRE	3.97	10.92	20.53	−6.75	−7.94	−24.21	0.33	0.39	**1.18***
	1 month	10.71	16.80							
	3 month	11.90	18.87							
	6 month	28.18	30.47							
Insomnia	PreIRE	19.05	21.01	29.38	−13.10	−20.11	−13.23	0.45	0.68	0.45
	1 month	32.14	33.01							
	3 month	39.15	32.02							
	6 month	32.28	29.94							
Appetite Loss	PreIRE	22.76	32.01	26.25	−2.03	1.63	3.66	0.08	0.06	0.14
	1 month	24.80	30.53							
	3 month	21.14	22.06							
	6 month	19.10	17.70							
Financial Difficulties	PreIRE	28.57	26.10	30.43	2.38	−15.48	18.65	0.08	0.51	0.61
	1 month	26.19	31.70							
	3 month	44.05	40.29							
	6 month	9.92	19.84							

The majority of statistically significant symptom scales changes occurred towards the later end of time points (i.e. 3 and 6 months post IRE), with only one scale (Diarrhea) showing statistical significance at 1 month, most likely due to the high incidence of tube-feed use and ongoing and worsening pancreatic exocrine deficiency (i.e. Creon management), since most to all of these patients had exocrine dysfunction pre-IRE. From these results we can see that additional therapies such as adjuvant chemotherapy and or adjuvant chemo-radiation therapy are contributing to these late QOL changes.

For this study Constipation, Diarrhea, Dyspnea and Insomnia showed statistical significance at either isolated single or multiple post-operative time points. This seemingly haphazard group of symptoms appears to be consistent with some of the symptoms associated with chemotherapy initiation and dosing, which has been previously reported. One study administered the same questionnaire to subjects receiving either trametinib or chemotherapy; the results of patients receiving chemotherapy showed similar changes in the symptom profile over time.[26] It is important to note this study found changes in functional assessment scales, but patients randomized to the chemotherapy arm received either DTIC or paclitaxel, whereas in this study there were no such limitations.[26] In addition, chemotherapy is known to affect multiple systems and thus cause many side effects. Further research is indicated to validate this potential explanation.

The standard protocol for patients undergoing IRE to treat LAPC at University of Louisville is to receive additional adjuvant chemotherapy.[7,19] More important is the timing of initiation for adjuvant chemotherapy. One study showed the efficacy and outcomes of chemotherapy had little difference as far as 12 weeks after surgery, but recurrence rates changed when patients did not complete chemotherapy cycles.[27].This study suggests it is more important to complete the chemotherapy cycles than to begin chemotherapy right after surgery.[27] Therefore, patients enrolled on this study typically would not begin adjuvant chemotherapy/chemo-radiation therapy until recovery from the IRE procedure, usually 4–6 weeks. Both the timing of recovery and percentage of patients undergoing adjuvant chemotherapy support the notion that the worsening symptom profile is likely due to chemotherapy toxicity and not necessarily the IRE procedure.

The ESAS data is different from the EORTIC data in that it asks about slightly different symptoms, but more importantly, asks about them in a different time frame. Therefore, the ESAS data places the EORTC data into perspective. There were small, statistically significant differences at the later end of post-operative time points for only 3 of the 9 categories measured; the majority of the data showed no statistically significant differences. Therefore, when patients were asked to reflect on their symptoms over a period of a week versus at that moment, they reported different results. This suggests that the relative importance of symptom severity to the patient is not as great. Thus the data supports the hypothesis that there would be no long term or permanent

Table 7
Effect size calculation table for the 9 categories found in the Edmonton Symptoms and Assessment Scale. No large effects sizes (ES > 0.8) noted.

Effect size (ESAS)										
Scale	Time point	Mean	SD	Common SD	Difference between means			Effect Size		
					PreIRE-1	PreIRE-3	PreIRE-6	PreIRE-1	PreIRE-3	PreIRE-6
No Pain	PreIRE	1.94	2.24	2.07	−0.12	−1.13	0.66	0.06	0.55	0.32
	1 month	2.06	2.01							
	3 month	3.07	2.41							
	6 month	1.28	1.52							
Not Tired	PreIRE	2.53	1.95	1.93	−0.98	−0.01	1.02	0.51	0.006	0.53
	1 month	3.51	2.55							
	3 month	2.54	1.62							
	6 month	1.51	1.42							
Not Nauseated	PreIRE	1.28	2.48	1.85	−0.03	−0.17	0.58	0.02	0.09	0.31
	1 month	1.31	2.05							
	3 month	1.45	1.60							
	6 month	0.70	0.88							
Not Depressed	PreIRE	1.69	1.75	2.11	−0.11	−0.38	0.99	0.05	0.18	0.47
	1 month	1.80	2.69							
	3 month	2.07	2.36							
	6 month	0.70	1.39							
Not Anxious	PreIRE	1.59	1.82	1.71	0.17	−0.14	1.08	0.10	0.08	0.63
	1 month	1.42	1.92							
	3 month	1.73	1.94							
	6 month	0.51	0.93							
Not Drowsy	PreIRE	1.63	2.18	2.60	0.17	−0.48	0.99	0.07	0.18	0.38
	1 month	1.46	2.21							
	3 month	2.11	2.42							
	6 month	0.64	1.22							
Best Appetite	PreIRE	2.50	2.76	2.29	−0.88	0.06	0.51	0.38	0.03	0.22
	1 month	3.38	3.02							
	3 month	2.44	1.82							
	6 month	1.99	0.94							
Best feeling of well- being	PreIRE	2.94	2.45	2.19	−0.16	−0.09	1.57	0.07	0.04	0.72
	1 month	3.10	2.56							
	3 month	3.03	2.21							
	6 month	1.37	1.31							
No shortness of breath	PreIRE	0.625	1.31	1.74	−1.32	−1.03	−0.62	0.75	0.59	0.36
	1 month	1.94	2.42							
	3 month	1.65	1.56							
	6 month	1.24	1.47							

*lower score better QOL.

detrimental quality of life changes when undergoing IRE therapy to treat LAPC.

Limitations to this study include, first, the limited definition for QOL used by the modules of the questionnaire. Given that QOL is subjective, additional research should include utilizing different metrics to define QOL, as well as aggregation with current results, to develop a more comprehensive understanding. Second, this is a single-center study, which could limit the generalizability to the entire population; therefore, a larger sample size should be used in future research. Finally, given the potential confounding variable of adjuvant chemotherapy administration, additional studies should control for this factor this in the study design.

Conclusions

In summary, the goal of this study was to examine the effects of IRE to treat LAPC on QOL, and results showed that there are no long-term QOL effects on patients treated for LAPC. Rather, the onset of symptoms, the statistically significant symptom profile, and the high percentage of patients undergoing adjuvant treatment all suggest that other interrelated clinical factors (e.g., chemotherapy toxicity) likely caused the results seen. In addition, the ESAS data suggests the relative importance of symptom severity may not be as great. Therefore, the initial hypothesis is not necessarily incorrect. We are confident that additional research examining the relationship between QOL changes in the use of IRE to treat LAPC will reveal substantive results that will continue to support our hypothesis.

Disclosure of financial interests and potential conflicts of interest

RCGM is a consultant for AngioDynamics. Wesley Field and Jack W. Rostas reported no biomedical financial interests or potential conflicts of interest. No outside support was received for this study.

Brief summary

Responses to quality-of-life and symptoms questionnaires indicated that constipation and insomnia increased at 3 months post-IRE, and diarrhea at 6 months. Analysis suggests that these symptoms were related to post-IRE therapies, and that IRE therapy does not adversely affect long term QOL in patients with LAPC.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjsurg.2019.03.020.

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