Metastatic renal cell carcinoma to the pancreas and other sites—a multicenter retrospective study

Cassandra Duarte,[a] Junxiao Hu,[a] Benoit Beuselinck,[b] Justine Panian,[c] Nicole Weise,[c] Nazli Dizman,[d] Katharine A. Collier,[e] Nityam Rathi,[f] Haoran Li,[f] Roy Elias,[g] Nieves Martinez-Chanza,[h] Tracy L. Rose,[i] Lauren C. Harshman,[j,p] Dharmesh Gopalakrishnan,[k] Ulka Vaishampayan,[l,q] Yousef Zakharia,[m] Vivek Narayan,[n] Benedito A. Carneiro,[o] Anthony Mega,[o] Nirmish Singla,[g,r] Cheryl Meguid,[a] Saby George,[k] James Brugarolas,[g] Neeraj Agarwal,[f] Amir Mortazavi,[e] Sumanta Pal,[d] Rana R. McKay,[c] and Elaine T. Lam[a,*]

[a]University of Colorado Cancer Center, University of Colorado Anschutz Medical Campus, 1665 Aurora Ct. MS F704, Aurora, CO 80045, USA
[b]Department of General Medical Oncology, University Hospitals Leuven, KU Leuven, Herestraat 49, 3000 Leuven, Belgium
[c]Moores Cancer Center University of California San Diego, San Diego, CA, USA
[d]City of Hope, Duarte, CA, USA
[e]The Ohio State University Comprehensive Cancer Center, Columbus, OH, USA
[f]The University of Utah Huntsman Cancer Institute, Salt Lake City, UT, USA
[g]University of Texas Southwestern Medical Center, Dallas, TX, USA
[h]Institut Jules Bordet, Brussels, Belgium
[i]UNC Lineberger Comprehensive Cancer Center, Chapel Hill, NC, USA
[j]Prior Institution: Dana-Farber Cancer Institute, Boston, MA, USA
[k]Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA
[l]Prior Institution: Karmanos Cancer Center, Detroit, MI, USA
[m]Holden Comprehensive Cancer Center at University of Iowa, Iowa City, IA, USA
[n]Abramson Cancer Center at the University of Pennsylvania, Philadelphia, PA, USA
[o]Legorreta Cancer Center at Brown University, Lifespan Cancer Institute, Providence, RI, USA
[p]Current Institution: Surface Oncology, Cambridge, MA, USA
[q]Current Institution: Rogel Cancer Center, University of Michigan, Ann Arbor, MI, USA

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Summary

Background Metastatic renal cell carcinoma (mRCC) is a heterogenous disease with poor 5-year overall survival (OS) at 14%. Patients with mRCC to endocrine organs historically have prolonged OS. Pancreatic metastases are uncommon overall, with mRCC being the most common etiology of pancreatic metastases. In this study, we report the long-term outcomes of patients with mRCC to the pancreas in two separate cohorts.

Methods We performed a multicenter, international retrospective cohort study of patients with mRCC to the pancreas at 15 academic centers. Cohort 1 included 91 patients with oligometastatic disease to the pancreas. Cohort 2 included 229 patients with multiples organ sites of metastases including the pancreas. The primary endpoint for Cohorts 1 and 2 was median OS from time of metastatic disease in the pancreas until death or last follow up.

Findings In Cohort 1, the median OS (mOS) was 121 months with a median follow up time of 42 months. Patients who underwent surgical resection of oligometastatic disease had mOS of 100 months with a median follow-up time of 52.5 months. The mOS for patients treated with systemic therapy was not reached. In Cohort 2, the mOS was 90.77 months. Patients treated with first-line (1L) VEGFR therapy had mOS of 90.77 months; patients treated with IL immunotherapy (IO) had mOS of 92 months; patients on 1L combination VEGFR/IO had mOS of 74.9 months.

Interpretations This is the largest retrospective cohort of mRCC involving the pancreas. We confirmed the previously reported long-term outcomes in patients with oligometastatic pancreas disease and demonstrated prolonged survival in patients with multiple RCC metastases that included the pancreas. In this retrospective study with heterogeneous population treated over 2 decades, mOS was similar when stratified by first-line therapy. Future research will be needed to determine whether mRCC patients with pancreatic metastases require a different initial treatment strategy.

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*Corresponding author.
E-mail address: Elaine.Lam@CUAnschutz.edu (E.T. Lam).
[r]Current Institution:Departments of Urology & Oncology, The James Buchanan Brady Urologic Institue, The John Hopkins School of Medicine, Baltimore, MD, USA.

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Research in context

Evidence before this study

The authors searched PubMed through January 2023 for papers using the terms "metastatic RCC" AND "pancreas" or "endocrine metastases" with no restrictions for language or date. The studies found were mostly retrospective reviews on the use of localized therapy for metastatic RCC to the pancreas. No prospective studies were found.

Added value of this study

Here we present a review on long-term outcomes of patients with metastatic RCC to the pancreas. We assess outcomes of a cohort with oligometastatic disease to the pancreas based on initial treatment type (surgery versus systemic therapy). We additionally assessed a second cohort of patients with metastatic disease that included the pancreas and evaluated outcomes based on type of first-line therapy.

Implications of all the available evidence

Our study confirms prior knowledge that RCC patients with pancreatic metastases generally have longer OS. In patients with oligometastatic RCC to the pancreas, treatment with systemic therapy or pancreatectomy both resulted in long overall survival. In patients with multiple metastases including to the pancreas, the median overall survival was long regardless of type of first-line systemic therapy. Prospective studies will need to be undertaken to establish the optimal first-line therapy (VEGFR inhibitor, IO, or combination therapy).

Introduction

Metastatic renal cell carcinoma (mRCC) is a heterogenous, lethal disease with an estimated five-year overall survival (OS) of 14%.[1] The Checkmate-214 trial has demonstrated the longest OS to date with median OS of 55.7 months for mRCC patients with intermediate- or poor-risk disease treated with first-line nivolumab and ipilimumab.[2,3] Renal cell carcinoma (RCC) patients with endocrine metastases, specifically pancreatic disease, have prolonged OS compared to patients with non-endocrine metastases.[1,4,5] Pancreatic metastases are uncommon, seen in only two to five percent of all malignancies including RCC, melanomas, colorectal carcinomas, breast cancers, and sarcomas.[6,7] RCC is the most common primary tumor leading to pancreatic metastases, with pancreatic metastases found in three to ten percent of metastatic RCC cases.[8]

For patients with oligometastatic RCC, the National Comprehensive Cancer Network (NCCN) Kidney Cancer Guideline recommendations include systemic therapy, metastasectomy, stereotactic body radiation therapy (SBRT), or ablative techniques.[9] The current literature on oligometastatic RCC pancreas tumors is comprised of individual case studies and small retrospective reviews, with most reviews looking at the utility of pancreatectomy as an option for disease management.[6,9–11] For isolated pancreas metastases, a partial or total pancreatectomy may be a feasible option for patients that are appropriate surgical candidates. Given that this can be a highly morbid surgery and some data demonstrates no clear OS benefit with surgery versus systemic therapy, there is interest in determining the role of non-surgical treatment options for patients with pancreatic oligometastatic disease.[12–14] SBRT, other ablative techniques, and systemic therapy are non-surgical treatments used based on patient factors, institutional resources, and provider experience. The optimal approach for treatment of mRCC to the pancreas has not been established.

For patients with mRCC to multiple organ sites including the pancreas, systemic therapy is the generally accepted approach. The biology of RCC with a predilection to the pancreas is incompletely understood. Metastatic sites of disease of RCC have heterogeneous biologic composition.[4] Recent work has suggested that pancreatic metastases of RCC have increased angiogenic activity and lower inflammatory burden.[15,16] These observations suggest that pancreatic metastases may have differential response to immunotherapy (IO) and vascular endothelial growth factor receptor (VEGFR) targeted therapy. However, there are no clinical trials to date comparing outcomes of patients with mRCC to the pancreas with differing systemic therapy modalities.

In this study, we report the long-term outcomes of patients with mRCC to the pancreas. In Cohort 1, we describe outcomes of systemic versus local therapy in patients with oligometastatic disease to the pancreas. In Cohort 2, we describe the long-term outcomes of systemic therapy in RCC patients with multiple sites of metastases including the pancreas.

Methods

Study design and patient population

We performed a multicenter, international, retrospective cohort study of patients with histologically proven mRCC involving the pancreas who were treated at 15 academic centers, 13 in the United States and two in

Europe, which are highly experienced in the management of RCC. Institutional review board (IRB) approval or exemption was obtained at each institution. Informed consent was not required per IRB as data collected was de-identified. Patients diagnosed and treated prior to January 2021 were included in the analysis. Data on patient demographics, tumor characteristics, local therapy, systemic therapy, and outcomes were collected using a de-identified data collection template with strict definitions for data collection to minimize inter-observer variation. No other restrictive inclusion criteria were applied. In Cohort 1, we evaluated local therapy versus systemic treatment in patients with oligometastatic disease to the pancreas. In Cohort 2, we evaluated outcomes of first-line (1L) systemic therapies including VEGFR, high-dose interleukin-2 (HD-IL2), immune checkpoint inhibitors (ICI), and combination VEGFR/IO in patients with mRCC including the pancreas.

Study endpoints

In Cohort 1, the primary endpoint was median OS from time of metastatic disease to the pancreas until death or last documented follow up. Secondary endpoints included time to initiation of systemic therapy from time of pancreas metastasis diagnosis for patients undergoing local therapy, and adverse events by treatment group. Presence of an adverse event was determined by individual sites with guidance in data collection tool from the coordinating site.

In Cohort 2, the primary endpoint was median OS from time of metastatic disease to the pancreas until death, or last documented follow up. Secondary outcomes included objective response rate (ORR) by local investigator assessment and time on treatment (TOT) with 1L therapy. Radiographic responses were assessed by local investigators and best response to treatment was characterized as complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD) or not evaluable (NE). TOT was defined as time from initiation of 1L therapy to discontinuation for any reason including progressive disease, toxicity, patient or practitioner preference, or death. Patients were followed from initiation of therapy until death or a data cutoff date of January 16, 2021, whichever occurred first. No formal sample size or power calculations were done *a priori* due to the retrospective nature of the study.

Statistical analysis

Descriptive statistics are presented for baseline characteristics of the entire patient population and by local versus systemic therapy for Cohort 1, and 1L treatment subgroup for Cohort 2. For continuous variables, the median and interquartile range (IQR) are reported and the non-parametric Kruskal Wallis test was conducted. For categorical variables, the frequencies and the percentages were calculated, and the chi-squared test was conducted. For OS, the survival probability was calculated by the Kaplan–Meier method. The survival curve and the median survival time are reported with the corresponding two-sided 95% Brookmeyer-Crowley's confidence interval if feasible. The median time and IQR were calculated for TOT. The cumulative frequencies estimated proportions, and the 95% simultaneous confidence intervals were calculated for the best radiographic responses to treatment.[17] The analyses for OS, TOT, and ORR were conducted for each cohort and subgroups within each cohort of the study. All statistical analyses were performed by an independent statistician to ensure unbiased data review. Analyses were conducted on R version 4.1.0, R Core Team (2021).

Role of the funding source

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C. Duarte, E. Lam, and J. Hu had full access to the dataset. The decision to publish was a joint consensus amongst all authors.

Results

Cohort 1

Ninety-one patients with oligometastatic disease only to the pancreas were identified. Four patients were excluded from analysis due to no treatment information provided, resulting in 87 patients in the final analysis (Fig. 1a). The median time from initial RCC diagnosis to development of oligometastatic disease in the pancreas was 97 months (range 46.5–153 months). 84 patients had prior nephrectomy (96.6%), 71 patients had non-metastatic disease at initial diagnosis (82.1%). 50 were International Metastatic Database Consortium (IMDC) favorable risk (59.5%) and 32 were intermediate risk (38.1%) at time of metastases. Median age at time of RCC diagnosis was 57 years. Median age at time of pancreatic oligometastatic disease was 65 years. Median year of RCC diagnosis was 2007 (range 2000–2011). Demographic data is further detailed in Table 1.

Forty-two patients (48.3%) underwent partial or total pancreatectomy (Table 2). Surgeries were performed at nine of the 15 academic centers with number of operations per site ranging from one to ten operations. 38 patients (43.7%) received systemic therapy as initial treatment for oligometastatic pancreas disease. Seven patients (8.0%) underwent SBRT therapy. Of the patients receiving systemic therapy, 23 received VEGFR, 9 received IO, 4 received combination VEGFR and IO, and 2 received mTOR inhibitor (Fig. 1a).

The median OS was 100.0 months (95% CI 93, not reached) in the surgery group and was not reached (95% CI 56, not reached) in the systemic therapy group (Table 3) with a median follow up time of 42 months for

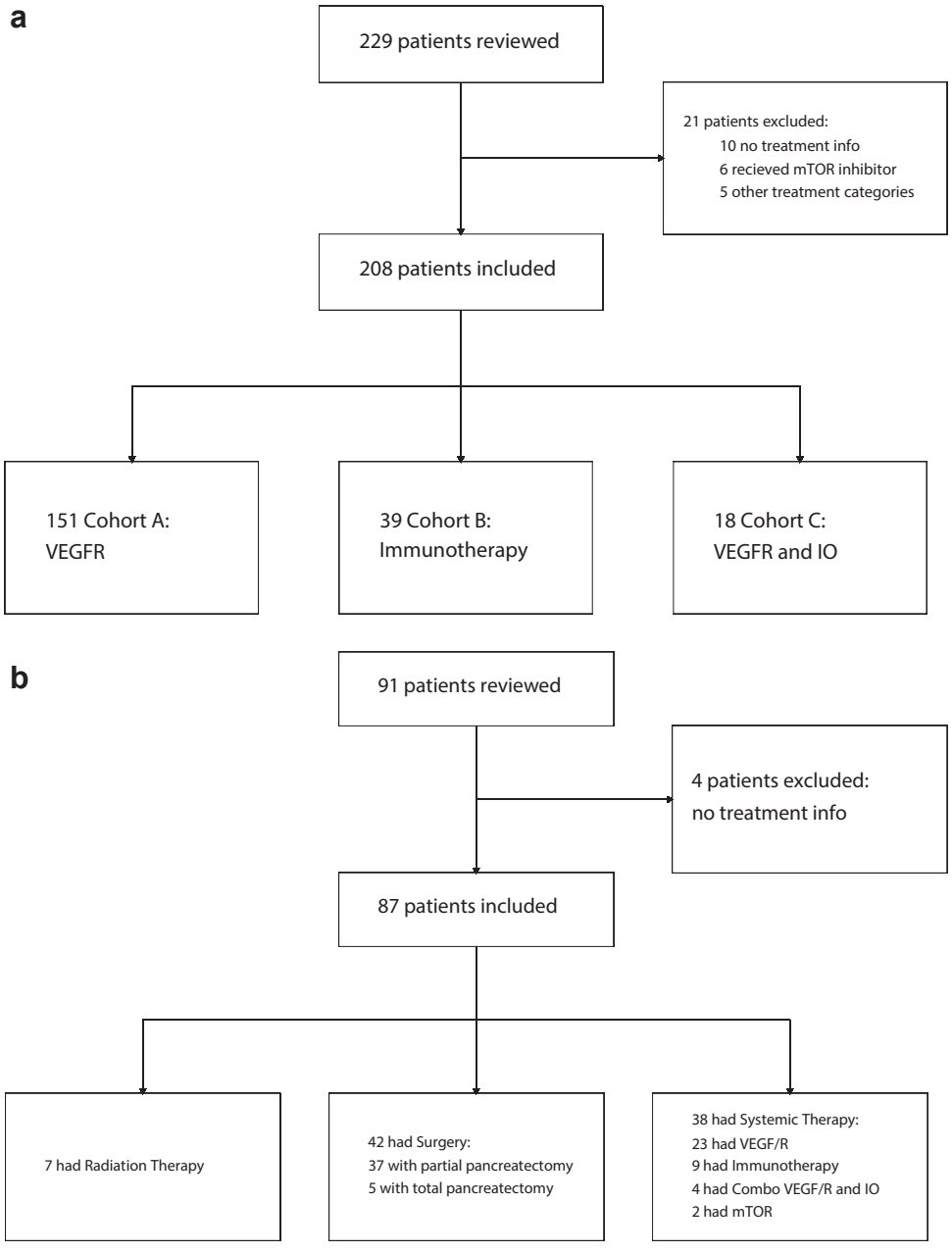

Fig. 1: **a Cohort 1 Study Population Consort Diagram. b Cohort 2 Study Population Consort Diagram.**

the entire study population. Primary endpoints were not calculated for the patients undergoing radiation therapy given the small sample size and lack of events.

Median time to initiation of systemic therapy in the surgery group was 19.5 months (IQR 4.8–40.9). In terms of adverse events, nine patients (22%) undergoing pancreatectomy required pancreatic enzyme therapy post-operatively and 12 patients (29.3%) required insulin post-operatively. For those treated with systemic therapies, the most common types of adverse events included gastrointestinal issues (19 patients, 50%), hypertension (10 patients, 26.7%), and dermatologic issues (5 patients, 13.3%).

Cohort 2

In Cohort 2, 229 patients with mRCC including pancreatic metastases were identified. Ten patients had not undergone any systemic treatment and were excluded from analysis. Six patients were treated with mTOR inhibitors as 1L treatment. Given the low

number, this treatment group was excluded from analysis. Five patients were treated with a 1L therapy that did not fall under the categorization of VEGFR, IO, or combination VEGFR/IO therapy. These patients were also excluded from analysis. This resulted in a study population of 208 patients in the final analyses (Fig. 1b). The median year of initial RCC diagnosis was 2009, with the median year of mRCC diagnosis being 2014 (range 2005–2015). 96 patients had synchronous disease (41.8%) and 111 patients had metachronous diease (55.8%). 65 patients (31.2%) had IMDC favorable risk, 89 (42.8%) had intermediate risk, and 24 (11.5%) had poor risk. Demographic data are further detailed in Table 1.

Of 208 analyzed patients, 151 patients (72.6%) received 1L VEGFR therapy, 39 patients (18.8%) received 1L IO therapy, and 18 patients (8.6%) received 1L combination VEGFR and IO therapy. Of the 39 patients receiving 1L IO therapy, 16 patients received HD-IL2, 21 patients received ICI therapy, and two patients received other IO (Fig. 1b). Patients in the VEGFR subgroup received a median of two lines of treatment in total. 71 patients (47%) treated with VEGFR as 1L therapy then received at least one form of IO as a subsequent treatment. Six patients (4%) who received VEGFR therapy were treated before 2004, 128 patients (84.8%) were treated between 2005 and 2017 and 17 patients (11.3%) were treated in 2018 or later. For the IO subgroup, 20 patients (51%) treated with IO as 1L therapy received at least one form of VEGFR as a subsequent treatment. Among patients who received IO therapy, one patient (2.6%) was treated before 2004; 31 patients (79.5%) were treated between 2005 and 2017 and 7 patients (17.9%) were treated in 2018 or later. The combination VEGFR/IO subgroup received a median of 1 total treatment line; many of the patients remained on combination therapy at time of data cut off. Among patients who received combination therapy, 1 patient (5.6%) was treated before 2004, 11 patients (61.1%) were treated between 2005 and 2017, and 6 patients (33.3%) were treated in 2018 or later.

The median length of follow-up was 52.5 months. At the time of analysis, 96 patients had died, and 112 patients were censored. The median OS was 90.7 months (95% CI, 74.9, 114) for the Cohort 2 total population (Table 3). When analyzed by 1L treatment subgroup, the IO subgroup had a median OS at 92 months (95% CI, 78, NR) with a median follow up time of 60.2 months. The VEGFR subgroup median OS was 90.8 months (95% CI, 74.9, 114) with a median follow up time of 53.6 months. For combination VEGFR and IO subgroup the median OS was 74.9 months (95% CI 33, NR) with a median follow up of 28.5 months (Fig. 2).

Given that the patients receiving IO spanned multiple decades during which advances in IO such as ICI were established, this subgroup of patients was further stratified by HD-IL2, ICI therapy, or other IO (Table 3). Median OS for patients on HD-IL2 was 89 months (95% CI 78, NR) with a median follow up time of 81.5 months and was not reached (95% CI) for patients on ICI therapy with median follow up of 39 months.

Demographic factors	Surgery N = 42	Radiation therapy N = 7	Systemic therapy N = 38	Total N = 87	p value
Sex					
Male	20 (47.6)	5 (71.4)	21 (55.3)	46 (52.9)	0.468
Female	22 (52.4)	2 (28.6)	17 (44.7)	41 (47.1)	
Race					
White	40 (95.2)	4 (57.1)	35 (92.1)	79 (90.8)	0.015
Black	1 (2.4)	2 (28.6)	1 (2.6)	4 (4.6)	
Asian	1 (2.4)	0 (0.0)	0 (0.0)	1 (1.1)	
Other	0 (0.0)	1 (14.3)	2 (5.3)	3 (3.4)	
Ethnicity					
Hispanic	3 (7.1)	0 (0.0)	5 (13.2)	8 (9.2)	0.441
Insurance status					
Private	14 (33.3)	2 (28.6)	11 (28.9)	27 (31.0)	0.991
Public	22 (52.4)	4 (57.1)	22 (57.9)	48 (55.2)	
Uninsured	– (–)	– (–)	– (–)	– (–)	
Other	6 (14.3)	1 (14.3)	5 (13.2)	12 (13.8)	
Histology					
Clear cell	42 (100.0)	6 (100.0)	38 (100.0)	86 (100.0)	–
Stage at diagnosis					
1	8 (25.8)	1 (20.0)	7 (22.6)	16 (23.9)	0.483
2	10 (32.3)	2 (40.0)	8 (25.8)	20 (29.9)	
3	10 (32.3)	2 (40.0)	7 (22.6)	19 (28.4)	
4	3 (9.7)	0 (0.0)	9 (29.0)	12 (17.9)	
Unknown	– (–)	– (–)	– (–)	– (–)	
Fuhrman grade at diagnosis					
1	4 (12.5)	0 (0.0)	0 (0.0)	4 (6.3)	0.411
2	13 (40.6)	3 (60.0)	12 (46.2)	28 (44.4)	
3	12 (37.5)	2 (40.0)	9 (34.6)	23 (36.5)	
4	3 (9.4)	0 (0.0)	5 (19.2)	8 (12.7)	
Unknown	– (–)	– (–)	– (–)	– (–)	
ECOG at diagnosis					
0	35 (94.6)	3 (75.0)	30 (90.9)	68 (91.9)	0.380
1	2 (5.4)	1 (25.0)	3 (9.1)	6 (8.1)	
2	– (–)	– (–)	– (–)	– (–)	
3	– (–)	– (–)	– (–)	– (–)	
Unknown	– (–)	– (–)	– (–)	– (–)	
IMDC Risk Category					
Favorable	27 (69.2)	6 (85.7)	17 (44.7)	50 (59.5)	0.128
Intermediate	11 (28.2)	1 (14.3)	20 (52.6)	32 (38.1)	
Poor	1 (2.6)	0 (0.0)	1 (2.6)	2 (2.4)	
Unknown	– (–)	– (–)	– (–)	– (–)	
MSKCC risk category at time of metastatic disease					
Low	24 (63.2)	5 (71.4)	15 (39.5)	44 (53.0)	0.239
Intermediate	13 (34.2)	2 (28.6)	22 (57.9)	37 (44.6)	
Poor	1 (2.6)	0 (0.0)	1 (2.6)	2 (2.4)	
Unknown	– (–)	– (–)	– (–)	– (–)	

Table 1: **Cohort 1 baseline characteristics of study population.**

Demographic factors	Subgroup A VEGFR N = 151	Subgroup B IO N = 39	Subgroup C VEGFR & IO N = 18	Total N = 208	p value
Sex					
Male	94 (62.3)	26 (66.7)	13 (72.2)	133 (63.9)	0.654
Female	57 (37.7)	13 (33.3)	5 (27.8)	75 (36.1)	
Race					
White	136 (90.1)	35 (89.7)	16 (88.9)	187 (89.9)	0.951
Black	2 (1.3)	0 (0.0)	0 (0.0)	2 (1.0)	
Asian	6 (4.0)	1 (2.6)	1 (5.6)	8 (3.8)	
Other	7 (4.6)	3 (7.7)	1 (5.6)	11 (5.3)	
Ethnicity					
Hispanic	20 (13.2)	4 (10.3)	2 (11.1)	26 (12.5)	0.866
Insurance status					
Private	38 (25.2)	24 (61.5)	10 (55.6)	72 (34.6)	0.001
Public	110 (72.8)	15 (38.5)	8 (44.4)	133 (63.9)	
Uninsured	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.5)	
Other	2 (1.3)	0 (0.0)	0 (0.0)	2 (1.0)	
Histology					
Clear cell	140 (92.7)	37 (94.9)	16 (88.9)	193 (92.8)	0.707
Stage at diagnosis					
1	16 (10.6)	8 (20.5)	2 (11.1)	26 (12.5)	0.210
2	15 (9.9)	3 (7.7)	4 (22.2)	22 (10.6)	
3	26 (17.2)	11 (28.2)	3 (16.7)	40 (19.2)	
4	42 (27.8)	9 (23.1)	6 (33.3)	57 (27.4)	
Unknown	52 (34.4)	8 (20.5)	3 (16.7)	63 (30.3)	
Fuhrman grade at diagnosis					
1	7 (4.6)	1 (2.6)	0 (0.0)	8 (3.8)	0.848
2	46 (30.5)	11 (28.2)	6 (33.3)	63 (30.3)	
3	47 (31.1)	11 (28.2)	4 (22.2)	62 (29.8)	
4	17 (11.3)	8 (20.5)	3 (16.7)	28 (13.5)	
Unknown	34 (22.5)	8 (20.5)	5 (27.8)	47 (22.6)	
ECOG at diagnosis					
0	88 (58.3)	26 (66.7)	12 (66.7)	126 (60.6)	0.802
1	26 (17.2)	6 (15.4)	2 (11.1)	34 (16.3)	
2	4 (2.6)	0 (0.0)	1 (5.6)	5 (2.4)	
3	1 (0.7)	1 (2.6)	0 (0.0)	2 (1.0)	
Unknown	32 (21.2)	6 (15.4)	3 (16.7)	41 (19.7)	
IMDC risk category					
Favorable	44 (29.1)	16 (41.0)	5 (27.8)	65 (31.2)	0.481
Intermediate	65 (43.0)	14 (35.9)	10 (55.6)	89 (42.8)	
Poor	17 (11.3)	6 (15.4)	1 (5.6)	24 (11.5)	
Unknown	25 (16.6)	3 (7.7)	2 (11.1)	30 (14.4)	
MSKCC risk category at time of metastatic disease					
Low	44 (29.1)	19 (48.7)	5 (27.8)	68 (32.7)	0.145
Intermediate	68 (45.0)	13 (33.3)	8 (44.4)	89 (42.8)	
Poor	11 (7.3)	5 (12.8)	2 (11.1)	18 (8.7)	
Unknown	28 (18.5)	2 (5.1)	3 (16.7)	33 (15.9)	
Prior nephrectomy					
No	65 (43.0)	14 (35.9)	8 (44.4)	87 (41.8)	0.574
Yes	81 (53.6)	25 (64.1)	10 (55.6)	116 (55.8)	
Unknown	5 (3.3)	0 (0.0)	0 (0.0)	5 (2.4)	
Timing of pancreatic metastases in relation to other metastases					
Synchronous	73 (48.3)	13 (33.3)	10 (55.6)	96 (46.2)	0.408
Metachronous	77 (51.0)	26 (66.7)	8 (44.4)	111 (53.4)	
Unknown	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.5)	

(Table 2 continues on next page)

Demographic factors	Subgroup A VEGFR N = 151	Subgroup B IO N = 39	Subgroup C VEGFR & IO N = 18	Total N = 208	p value
(Continued from previous page)					
Local treatment for pancreatic metastases					
No	129 (85.4)	32 (82.1)	16 (88.9)	177 (85.1)	0.778
Yes	22 (14.6)	7 (17.9)	2 (11.1)	31 (14.9)	
Type of local treatment if applicable					
Pancreatectomy	16 (72.7)	5 (71.4)	2 (100.0)	23 (74.2)	0.787
SBRT	5 (22.7)	1 (14.3)	0 (0.0)	6 (19.4)	
Radiation therapy	1 (4.5)	1 (14.3)	0 (0.0)	2 (6.5)	
Median number of total lines of systemic therapy					
Median (IQR)	2.0 (2.0–4.0)	2.0 (1.0–4.0)	1.0 (1.0–2.0)	2.0 (1.0–4.0)	0.004
Total lines of systemic therapy					
1	31 (20.5)	12 (30.8)	11 (61.1)	54 (26.0)	0.024
2	45 (29.8)	13 (33.3)	4 (22.2)	62 (29.8)	
3	29 (19.2)	3 (7.7)	1 (5.6)	33 (15.9)	
4	26 (17.2)	5 (12.8)	1 (5.6)	32 (15.4)	
5 or more	20 (13.2)	6 (15.4)	1 (5.6)	27 (13.0)	

Table 2: **Cohort 2 baseline characteristics of study population.**

204 patients were included in the TOT analysis; four patients were excluded due to missing data. The median TOT was 10 months (IQR 3.69–22.1) for the total population. Table 4 demonstrates the TOT by treatment subgroup and Table 5 shows the TOT by IO subtype. Patients in the combination VEGFR and IO subgroup had a median TOT at 15 months (IQR 5.7, 21.3) while patients in the IO group had aTOT at 6.5 months (IQR 3, 10). Best radiographic response and TOT was examined by IMDC risk category and treatment subtype. Of 126 patients receiving 1L VEGFR therapy, 44 favorable risk patients had a median TOT of 13.5 months (6.6–29.2) and ORR of 48.8%. Of the 36 patients receiving 1L IO, the six poor risk patients had a median TOT of 10.3 months (4.5–22.5) with 83.3% ORR (Supplemental Tables S1 and S2).

Population	Median OS (months) 95% CI	Median follow up time (months)
Total Cohort 1 population	121 (93, NR)	42
Surgery	100 (93, NR)	
Systemic therapy	NR (56, NR)	
Total Cohort 2 population	90.77 (74.9, 114)	52.5
Cohort A—VEGFR	90.77 (66, 114)	53.6
Cohort B—IO	92 (78, NR)	60.2
HD-IL2 Therapy	89 (78, NR)	81.6
ICI Therapy	NR (NR, NR)	39
Cohort C—VEGFR/IO	74.9 (33, NR)	28.5

NR Indicates not reached.

Table 3: **Median overall survival of Cohorts 1 and 2.**

181 patients were included in the best radiographic response analysis; 27 patients were excluded due to missing data. Across all 1L treatments, seven patients demonstrated a complete response (3.9%), 74 patients had partial response (40.9%), 83 patients had stable disease (45.9%), and 17 patients had progressive disease (9.4%) as their best response to 1L therapy. Tables 4 and 5 show the breakdown of best radiographic response and time on treatment by treatment type. The ORR were 46.6% (60 patients), 36.1% (13 patients), and 50% (8 patients) for the VEGFR, IO, and VEGFR/IO groups, respectively. The clinical benefit rate was 90.7% for the total population, 93.1% for VEGFR subgroup, 77.8% for IO subgroup, and 100% for the combination VEGFR/IO subgroup.

Discussion

To our knowledge, this is the largest retrospective cohort of mRCC involving the pancreas to date. In this retrospective, multi-institutional study, we confirmed the previously reported favorable long-term outcomes in patients with oligometastatic pancreas disease and established similar prolonged survival in patients with multiple organ RCC metastases that include the pancreas. The median OS in patients with oligometastatic pancreatic only disease was 100.0 months after partial or total pancreatectomy and not reached for patients on systemic therapy. In patients with multiple metastases including the pancreas, the OS from the time of metastatic diagnosis was 90.8 months. Prolonged OS of mRCC to the pancreas is well documented with previous reports of OS of 42–106 months.[5,8,18,19] This is in contrast with shorter OS for mRCC patients

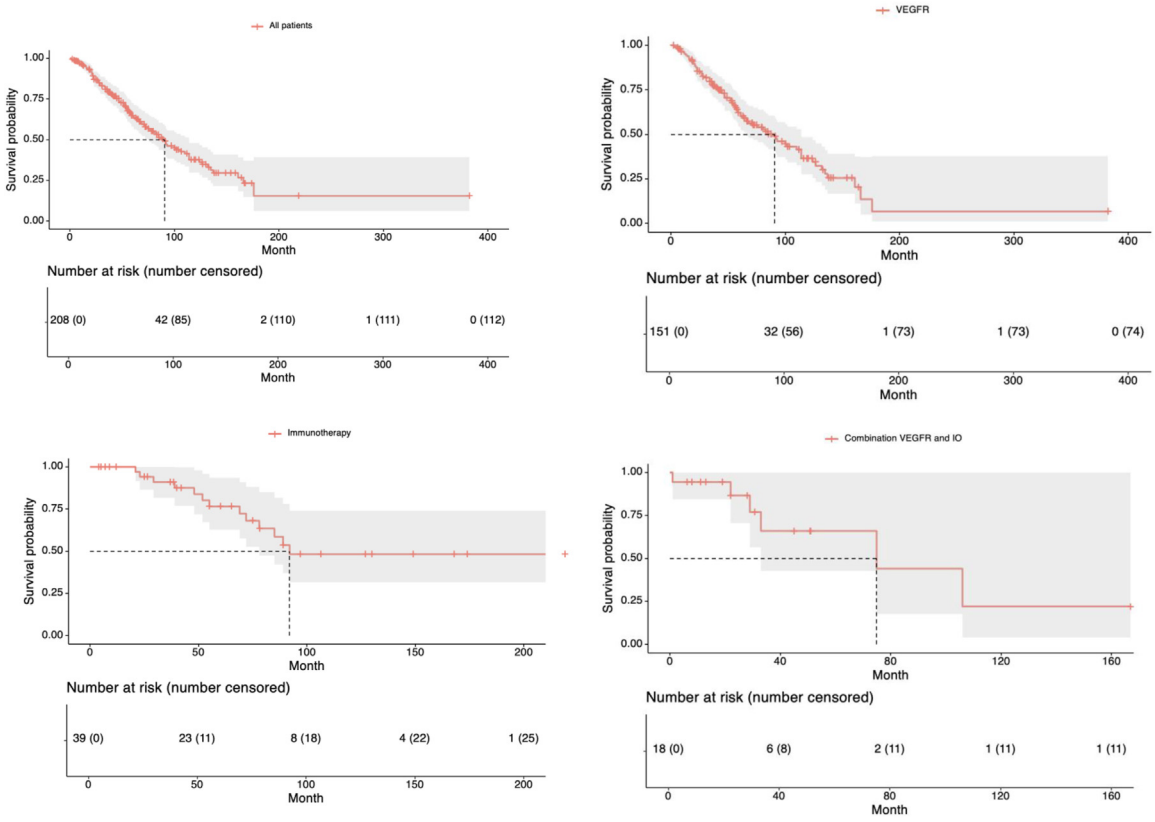

Fig. 2: **Kaplan meier curves of overall survival for Cohort 2 total population and by subgroup.**

in general, with the longest median OS currently reported at 57.7 months.[2,3,20]

In Cohort 1, we OS was numerically similar regardless of treatment with surgery versus systemic therapy for patients with oligometastatic pancreas recurrences, though direct statistical comparision was not made. In accordance with NCCN guidelines, patients with oligometastatic disease are eligible for a variety of treatment options including metastasectomy, SBRT, ablation, or systemic therapy including combination VEGFR/IO therapy.[21–24] NCCN guidelines state that sites amenable to metastasectomy include brain, lung, and bone metastases; pancreatic lesions are not specifically mentioned.[9] Presently, there are diverse practice patterns with regards to management of pancreatic lesions.[25] Pancreatectomy is associated with high morbidity and many providers and patients opt against surgery. Our findings suggest that systemic therapy could bea reasonable approach for patients with oligometastatic disease of the pancreas, though prospective work will need to be done to establish direct statistical significant between treatment modalities.

In Cohort 2, we evaluated the impact of systemic therapy regimen (VEGFR, IO, or VEGFR/IO) in the 1L setting on OS, ORR, best response, and median TOT. The median OS was 90.8 months in patients treated

Outcome		VEGFR subgroup	Immunotherapy subgroup	Combination VEGFR/IO subgroup	Total population
Best radiographic response Frequency (N (%))	CR	2 (1.6)	5 (13.9)	0 (0.0)	7 (3.9)
	PR	58 (45.0)	8 (22.2)	8 (50.0)	74 (40.9)
	SD	60 (46.5)	15 (41.7)	8 (50.0)	83 (45.9)
	PD	9 (7.0)	8 (22.2)	0 (0.0)	17 (9.4)
Median time on treatment (months, IQR)		11.6 (4.0, 28.1)	6.5 (3.0, 10.0)	15.0 (5.7, 21.3)	10.0 (3.7, 22.1)

Table 4: **Cohort 2 best radiographic response and time on treatment by subgroup.**

with 1L VEGFR therapy, 92 months with 1L IO therapy, and 75 months with 1L VEGFR/IO therapy. Given the retrospective and observational nature of this study, direct statistical comparison of treatment line outcomes was not performed. Approximately 50% of patients in the 1L VEGFR and IO groups received subsequent IO or VEGFR therapies, respectively, indicating that access to a subsequent therapy did not seem to be a confounding factor in mOS. Within the IO group, patients treated with HD-IL2 had a CR rate of 18.8% and TOT of 7.5 months. The CR rate of ICI 1L patients 5.6% and TOT was 4.3 motnhs. However, as HD-IL2 is no longer commonly used it is unclear the significance of this finding.

The Cohort 2 population had a CR rate with IO therapy of 13.9% and ORR with VEGFR-based regimens of 46.6% for VEGFR alone, and 50% for VEGFR/IO. The IO therapy alone CR was 36.1%. The median TOT for 1L therapy in Cohort 2 was 15 months for the-VEGFR/IO therapy cohort, and 6.5 months for IO alone with the total population TOT reaching 10 months. This is consistent with recent studies of VEGFR/IO combination studies showing improved median progression free survival over VEGFR monotherapy in the mRCC population.[26,27]

Significant work has investigated angiogenesis inhibition in metastatic tumors. In a comprehensive review of tumor angiogenesis, Fidler and Kripke explain how metastatic disease requires an established blood supply and argue that rather than inhibiting de novo angiogenesis, existing tumor capillary networks should be the target of novel therapeutic agents.[28] Pancreatic RCC metastases have demonstrated heightened angiogenesis, and enrichment for PBRM1 mutations and concomitant decrease in BAP1 mutations, and an uninflamed stroma.[15] In a study of 654 mRCC patients with metastases to the pancreas, liver, brain or lung found the 58 patients with pancreatic metastases had greater *PBRM1* alterations (52% versus 25%) compared to patients with other sites of metastases. Patients with pancreatic metastases had a non-immunogenic phenotype with a lower prevalence of B cells and a higher proportion of NK cells present on histology, and lower rates of PD-L1 positivity (7% compared to 25%, p = 0.03).[16] Given the difference in OS based on site of metastases, researchers have performed histologic analysis of pancreatic metastases of RCC patients. In an analysis of 31 patients with mRCC to the pancreas, patients demonstrated potential sensitivity to antiangiogenic agents and resistance to ICI therapy.[15] Genomic analysis of primary tumors from the cohort revealed favorable mutations in *PBRM1*, 3p loss, and 5q amplification were common whereas more aggressive mutation such as *BAP1*, loss of 9p, 14q and 4q were less common.[15] Pancreatic metastases had a distinct molecular profile with higher rates of *PBRM1*, *ALK*, and *NTRK3* alterations and lower rates of *CDKN2A*, *BAP1* and *MTAP* alterations, and lower PD-L1 positivity.[16]

Outcome		High dose IL-2 therapy	Checkpoint inhibitor therapy
Best response to 1st line therapy (N (%))	CR	3 (18.8)	1 (5.6)
	PR	1 (6.2)	7 (38.9)
	SD	6 (37.5)	8 (44.4)
	PD	6 (37.5)	2 (11.1)
Time on 1st line therapy (Month)	Median (IQR)	7.5 (3.8, 9.2)	4.3 (2.7, 13.0)

Table 5: **Cohort 2 best radiographic response and TOT by IO subtype.**

These studies demonstrate that the inherent mechanism of pancreatic metastases in mRCC may differ from other sites of disease. Pancreatic metastases may have a less immunogenic phenotype which may be important in determining future therapeutic options. These observations generate one hypothesis that VEGFR treatment may be more effective than IO for this population, as has been previously suggested. In a retrospective review of over 10,000 mRCC patients treated from 2002 to 2019 it was demonstrated that OS of patients with pancreatic metastases was greatest at 44.7 months (95% CI 36.4, 50.0) compared to the OS of 16 months (95% CI 13.7, 18.8) for patients with pleural metastases.[4] Consistent with previous observations, we found that TOT for ICI was 4.3 months compared to 11.6 months with VEGFR.

This data argues for future histological work to be done on a larger study population to determine if this finding of antiangiogenic responsiveness holds. We are currently evaluating tissue biomarkers of mRCC in patients with pancreas metastases to better understand the biology of these tumors. If data demonstrates a predilection for tumor response to certain therapies, this will allow for further prospective trial work to be done on personalization of cancer directed therapy based on metastatic site of disease. Analysis of tissue markers in conjunction with laboratory review of patients with oligometastatic disease will hopefully result in the development of prognostic models for RCC patients with metastatic disease to guide ideal therapeutic regimens going forward.

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Our study had several limitations. The retrospective study design could have introduced multiple selection

biases. While data were collected on possible confounding factors that may have affected OS, such as crossover between VEGFR and IO in subsequent lines of treatment and local treatment administered for pancreatic metastases, the retrospective nature of this study limits a study of causality between these factors. As our patient population spanned over twenty years of diagnoses, we acknowledge that the treatment landscape for mRCC has changed significantly during this time with the advent of VEGFR and ICI. Prior to 2005, cytokine-based treatments including HD-IL2 were standard of care. Between 2005 and 2015, patients were treated with VEGFR and mTOR inhibitors in the targeted therapy era. The approval of nivolumab in 2015 heralded the ICI era for mRCC and multiple combination therapies have been approved in the 1L setting since 2018.[29] Development and use of evolving novel therapies may have affected OS for various subgroups. Median follow up time was shorter for the Cohort 2 subgroups receiving immune checkpoint inhibitor therapy and combination VEGF/IO therapy due to the fact that these lines of therapy have not been approved for mRCC as long as single agent VEGFR. Therefore, true median overall survival may be longer for patients with mRCC treated with these options; however, a longer follow up period will be needed to determine this.

Another limitation is our small sample size of patients undergoing radiation therapy for pancreatic metastases, precluding further analysis on outcomes for this treatment subgroup. Given that prior studies have demonstrated the validity of SBRT to oligometastatic disease, it will be necessary to study outcomes of larger cohorts of patients undergoing radiation therapy in comparision with surgical intervention and systemic therapy.

Data collection was standardized between institutions with a common data dictionary and data collection template, but each institution was responsible for independent data collection. Bias may have affected data collection given that multiple individuals were responsible for collection. Additionally, the data regarding best radiographic response to treatment was determined by individuals at each institution. Radiographic images were not collected from each site for central or blinded review. Given the retrospective nature of this study there were mssing data which may have affected our outcomes. The nature of a retrospective chart review across multiple decades, instituions, and treatment types limited the ability for direct comparision between the treatment subtypes.

In conclusion, our work represents the largest review of patients with mRCC to the pancreas examining OS based on 1L systemic therapy. Our study, which included patients treated with contemporary ICI and combinations, confirms prior knowledge that individuals with pancreatic metastases generally have longer OS and improved time on therapy with VEGFR. In this retrospective study with heterogeneous population treated over two decades, there were no statistically significant mOS differences noted when stratified by first-line therapy. Future research will be needed to determine whether mRCC patients with pancreatic metastases require a different initial treatment strategy.

Contributors

E. Lam was responsible for study idea and gathering collaborators in addition to guiding statistical analysis and contributing to manuscript. C Duarte was responsible for primary manuscript writing, data collection and organization and organizing collaborators. J Hu was primarily responsible for data analysis. E Lam and C Duarte had access to and verified data. All remaining authors were responsible for data collection from their respective institutions, and provided editoral comments on drafts of manuscripts.

Data sharing statement

The de-identified data for Cohorts 1 and 2 will not be published but if researchers are interested in reviewing data, the corresponding author can be contacted.

Declaration of interests

ETL has received institutional research support from Amgen, Inc., Argos Therapeutics, Arrowhead Pharmaceuticals, Inc., Astellas Pharma, Inc., Bristol Myers Squibb, Biosplice Therapeutics, Inc., Calithera Biosciences, Constellation Pharmaceuticals, Inc., Exelixis, Forma Therapeutics, Genentech/F. Hoffmann-La Roche Ltd, Janssen Pharmaceuticals, Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., OnQuality Pharmaceuticals LLC, Peloton Therapeutics, Pfizer, Inc., Promontory Therapeutics, Inc (formerly Phosplatin).

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LH reports grants to prior institution from Bristol-Myers Squib, Merck, and Takeda. As well as current employment (including stock options) at Surface Oncology outside the submitted work. LH reports advisory or consulting services for Genentech, Pfizer, Corvus, Merck, Exelixis, Novartis, Jounce, Bristol-Myers Squibb, EMD Serrano. LH reports honoraria for lectures/presentations for Michael J Hennessy Associates (Healthcare Communications Company and several brands such as OncLive and PER), ASIM CME, and Ology Medical Education. LH receives support from Genentech for travel outside of the submitted work.

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RM reports consulting fees from Aveo, AstraZeneca, Bayer, BMS, Calithera, Caris, Dendreon, Exelixis, JNJ, Novartis, Merck, Myovant, Pfizer, Sanofi, Sorrento Therapeutics, Telix, Tempus.

VN reports institutional research funding from Pfizer, Merck, Jenssen, Bristol Myers Squibb. BN reports consulting fees from Merck, Janssen, Myovanat Sciences, Exelixis. BN reports honoraria from Pfizer.

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NM reports participation in data safety monitoring board or advisory board for MDS, Ipsen, BMS, and Astellas.

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All other authors have nothing to declare.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.102018.

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