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Review

Isolated Pancreatic Metastases of Renal Cell Carcinoma—Clinical Particularities and Seed and Soil Hypothesis

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Simple Summary: A meta-analysis of 1470 isolated pancreatic metastases of renal cell carcinoma revealed that these are characterised by not only the exclusive occurrence of PM and a good prognosis but a lack of prognostic significance of volume and growth rate dependent risk factors and the independence of treatment results from standard or local resections. The good prognosis affects not only isolated PM, but also multi-organ metastases of the RCC, in which the additional occurrence of PM is also associated with a better prognosis. As an explanation for all these peculiarities, a strong acting seed and soil mechanism can serve, which allows metastases settlement only in the pancreas, but prevents them definitively or for years in all other organs. Genetic studies revealed specific changes in cases of PM of RCC and a lack of loss of 9p and 14q, which are otherwise specific gene mutations at the onset of generalization, a low weight genome instability index, and a low rate of PAB1 and a high rate of BPRM1 alterations, which signal a more favourable course. The cause of pancreatic organotropism in isPMRCC, however this is still unclear.

Abstract: A meta-analysis of 1470 isolated pancreatic metastases of renal cell carcinoma revealed, that, in addition to the unusual exclusive occurrence of pancreatic metastases and the favourable treatment results, the isPMRCC is characterised by further peculiarities of the clinical course: The lack of prognostic significance of volume and growth rate dependent risk factors and the independence of treatment results from standard or local resections. As an explanation for all these peculiarities, according to today's knowledge, a strong acting seed and soil mechanism can serve, which allows embolized tumour cells to grow to metastases only in the pancreas, and prevents them definitively or for years in all other organs. The good prognosis affects not only isolated PM, but also multi-organ metastases of the RCC, in which the additional occurrence of PM is also associated with a better prognosis. Genetic studies revealed specific changes in cases of PM of RCC: Lack of loss of 9p21.3 and 14q31.2, which are otherwise specific gene mutations at the onset of generalization, a low weight genome instability index, i.e., high genetic stability, and a low rate of PAB1 and a high rate of BPRM1 alterations, which signal a more favourable course. The cause of pancreatic organotropism in isPMRCC is still unclear, so only those factors that have been identified as promoting organotropism in other, more frequent tumour entities can be presented: Formation of the pre-metastatic niche, chemokine receptor–ligand mechanism, ability to metabolic adaptation, and immune surveillance.

Keywords: renal cell carcinoma; pancreatic metastasis; risk-factors; seed and soil mechanism

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1. Introduction

Isolated pancreatic metastases (isPM) are a rare and unusual metastasis course of renal cell cancer (RCC), in which metastases occur only and exclusively in the pancreas, either definitively or over a long period of time. In addition, studies in recent years have shown that there are still other peculiarities of the clinical course in this entity that are not otherwise observed in metastasizing RCC. In addition to the extraordinarily favourable

outcome, these features include the lack of prognostic significance of tumour volume and tumour growth rate dependent risk factors and the lack of influence of the extent of surgical therapy (local versus standard resections). Based on a comprehensive literature review with meta-analysis, the present study provides an overview of the totality of these characteristics, presents and analyses the present data and discusses the possible relationship of these characteristics to the seed and soil mechanism (SSM).

2. Material and Methodology

A systematic review was performed following PRISMA guidelines. The literature data were obtained from the MEDLINE (PubMed) database from 1952 (first description of an isPM [1]) to 1 October 2022. The search criteria were: Renal cell carcinoma and pancreatic metastasis. Inclusion criteria were casuistic reports and single and multicentre institutional reports about isPM that occurred synchronously or metachronous to the RCC diagnosis and did not have additional organ metastases at the time of isPM diagnosis or within 6 months before or after isPM diagnosis and which were termed isolated pancreatic metastases of RCC (isPMRCC). In order to minimize the potential risk inherent in analysing small numbers of cases, only those single and multicentre institutional reports that included 20 or more cases were included in the results. These works are called high volume studies. Exclusion criteria, and vice versa, were non-RCC pancreatis metastases, observations with missing histology and widespread metastatic disease. In isPMRCC reports all observations in which other organ metastases were present in addition to the PM or had occurred within 6 months before or after the isPM diagnosis were excluded from the examination. In the few cases where an institution published its results several times over the years (Johns Hopkins University School of Medicine; Verona University of Verona Hospital Trust; Dept. of Surgery University of Heidelberg; Dept. of Surgery, Memorial Sloan-Kettering Cancer Institute), the most detailed report was accepted for the analysis and the others excluded.

In addition to publications that are limited exclusively to isolated pancreatic metastases, there are also several papers that included isolated PM as well as individual cases of PM with synchronous-resectable, extrapancreatic metastases in their investigations if an R0 situation could be achieved and analysed in the two groups together as one collective. However, this is methodologically problematic for the questions raised here, since it is not certain that both groups exhibit identical clinical behaviour. The inclusion of this works in the isolated PM group of the RCC was therefore refrained from. In order not to lose completely the information contained in these publications, these reports are recorded and analysed as a separate group ("PM with synchronously resected extrapancreatic metastases"). However, to also limit the influence of extrapancreatic metastases on the results to a reasonable level in this group, all those publications were excluded in which the proportion of additional extrapancreatic lesions was >20%. In this way, a total of 1470 isPMRCC observations were compiled [1–254] (isolated PM of the RCC 565 casuistic observations, 489 in single and multicentre reports and 416 isPM in publications where in some cases additional synchronously resected extrapancreatic metastases existed), which form the basis of a meta-analysis (Figure 1).

In these groups, the influence of tumour volume-related risk factors (singular versus multiple PM, number and size of PM), growth rate dependent risk factors (synchronous versus metachronous PM, interval between RCC treatment and PM diagnosis) and extent of surgery on outcome was determined. It is in the nature of a retrospective study that not all relevant study details were provided in all cases included. The actual number of cases which can be used for each analysis is therefore given in each case. An analogous approach was taken when calculating the influence of time to metastasis onset and metastasis size. Only singular metastases were used in the calculations of metastases size. Standard resections were partial DP, distal pancreatectomy and total DP; local resections were operations described as metastasis enucleation/resection/extirpation and midsegment resection.

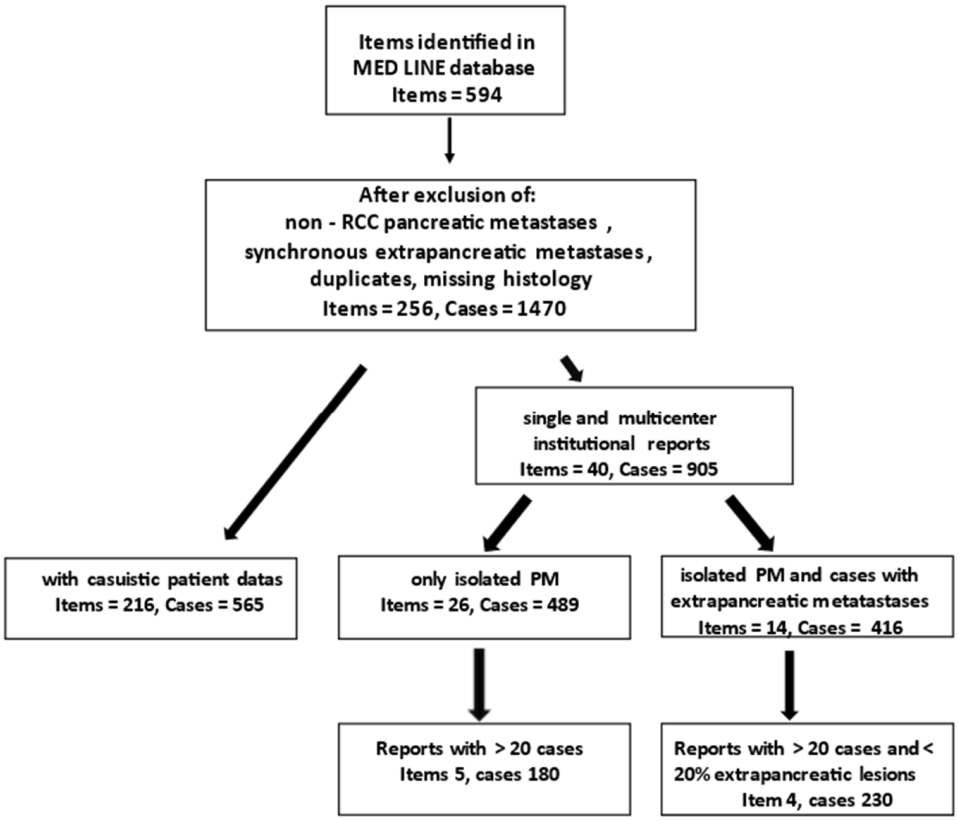

Figure 1. Search and selection strategy.

Statistics

Kaplan-Meier curves were plotted with differences between strata determined by log rank tests. A Cox proportional hazard regression analysis was applied to determine the influence of possible risk factors on survival, such as the number and diameter of metastasis and the time interval until the occurrence of isPMRCC. Hazard ratio and their 95% confidence intervals (IV) were reported. A p-value < 0.05 was considered statistically significant. Statistical analyses were performed with SPSS, version 25.0 (SPSS, Chicago, IL, USA).

3. Results

3.1. TreatmentOoutcomes

3.1.1. Surgical Therapy

Depending on the location and number of PM as well as the general condition of the patient, this was performed as partial or total duodenopancreatectomy, distal pancreatic resection, central pancreatectomy and local tumour resection. From 421 cases reported casuistically, a cumulative 5- and 10-year survival rate (SR) of 75.7% and 48.4%, respectively, can be calculated (Figure 2). In single and multicentre institutional reports of isolated PM [99,143,183,185,191,201,209,216,234], comparable results were reported with five-year SR of 52%–84%, 53% [99], 61% [143], 52% [183], 72% [184], 56% [190], 71% [200], 69% [208], 80% [215], 84% (Median 72%) [233]. 10a: 63% (median 69%) [254]. This also applies to the reports that additionally included cases with synchronously resected extrapancreatic metastases in their analyses [134,176,181,191,195,211,229,232,235,239,242,243] 88% [134]; 77% [176]; 63% [181], 79% [191], 72% [195], 50% [211], 72% [232], 79% [235], 81% [239], 68% [242], 83% [243], 77% [229]. 10a Schwarz 32%, Milanetto 55%: five-year SR 50–88% (median 77%).

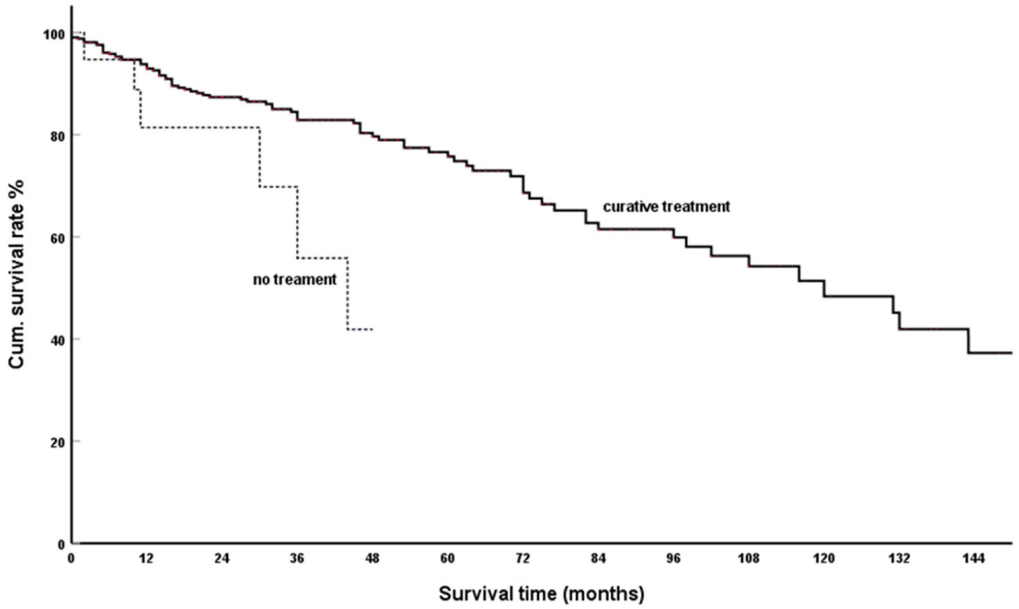

Figure 2. Surgical treatment vs. non-treatment group; Kaplan-Meier survival curves (p = 0.013).

3.1.2. Spontaneous Course of IsPMRCC

In Figure 2, we also present the results of the few observations that were not administered surgically or targeted therapy (TKI, m-tor inhibitors or immunotherapy). The three-year SR of 56% calculated from 19 casuistically reported observations [10,22,63,64,78,90,107,166,175,185,188,194,216,250] is a favourable result for the spontaneous course of a metastatic RCC. However, the result is significantly worse than after interventions with curative intent (p = 0.013).

3.1.3. Systemic Treatment

Since the introduction of targeted therapies in the form of tyrosine kinase inhibitors (TKI), M-Tor inhibitors (MTI) and Immune Checkpoint Inhibitors (ICI) such as Anti PD1 and Anti PD1L and AntiCTLA4, effective drug therapy has been available in advanced RCC. These agents revolutionized the systemic treatment of mRCC and caused a significant prolongation of progression free survival and OS, which also affected the PM of the RCC [158,175,204,255–258]. Santoni et al. [189] compared TKI treatment with surgical treatment in a large retrospective multicentre study of 103 PM of the RCC with 95% isolated PM in the resected cases and 24% in the systemic treated patients. With a median OS of 103 months versus 86 months, the difference between resected and unresected patients was not significant in terms of overall survival (OS). The good response of the isPMRCC to TKI, however, as Singla et al. [238] was able to show, is contrasted with a refractoriness to ICI. Both results: the good response to TKI and the nonresponse to ICI could be explained by the enrichment of angiogenic markers and low levels of inflammatory biomarkers in PM observations [238].

3.2. Tumour Volume-Dependent Risk Factors

3.2.1. Single Versus Multiple Metastases

From 396 sufficiently documented casuistic observations, a cumulative five-year SR of 70.4% and 79.6%, respectively, for single and multiple metastases was calculated (Figure 3). The difference in survival time is not significant (p = 0.162).

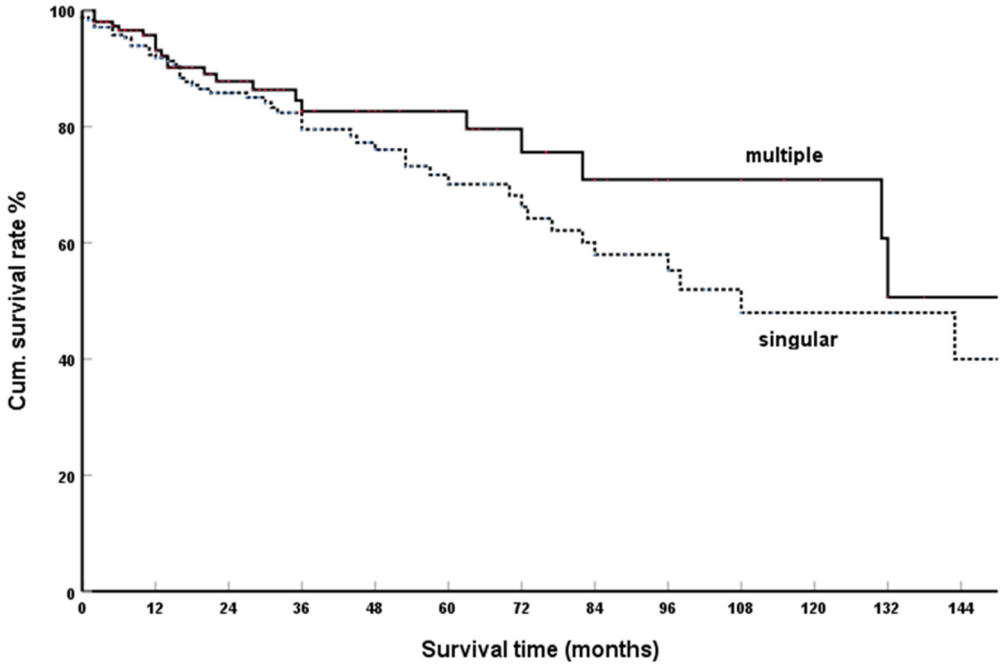

Figure 3. Solitary vs. multiple isPMRCC; Kaplan-Meier survival curves (p = 0.162).

In high volume single and multicentre reports and literature reviews of isolated PM, it was also reported that single or multiple occurrence of PM has no significant influence on the OS: Konstantinidis et al. [143], N = 20, n. s. (p = 0.87); Tosoian et al. [183], N = 42, n. s. (p = 0.727); Benhaim et al. [184], N = 20, n. s. (p value not specified); Anderson et al. [215], N = 20, n. s. ($p > 0.05$); Malleo et al. [245], N = 69, n. s. (p = 0.77); Reddy et al. [259], N = 21, n. s. Similar results were found in the reports, which included cases of PM with synchronously resectable extrapancreatic metastases in addition to isolated PM: Schwarz et al. [181], N = 62, n. s. (p = 0.9); Di Franco et al. [232], N = 21, n. s. (p = 0.391); Milanetto et al. [235], N = 39, n.s. (p = 0.9); Blanco-Fernández et al. [243], N = 116, n. s. (p = 0.81).

In summary, it can be seen that both in the casuistic observations and in the high volume single and multicenter reports, both in the group of isolated PM and in the group that added to isolated PM also individual observations of PM with resectable extrapancreatic metastases, there was no influence of single or multiple occurrence of PM on the SRs.

3.2.2. Number of Pancreatic Metastases

From 336 analysed casuistic observations, no relationship could be found between the number of PM and SR (HR 0.916; 95% IV 0.730–1.135; p = 0.419). The only major institutional report that examined this question (in a group that added to isolated PM also individual observations of PM with resectable extrapancreatic metastases) also showed no influence of the PM number on the SR: Di Franco et al. [232], N = 21, n. s. (p = 0.823).

3.2.3. Size of PM

Adequate information was available for 253 casuistic communications. Analysis showed that there was no relationship between metastasis size and survival: HR 1. 014, 95% IV 0. 999–1. 028; p = 0.188. Large single and multicentre reports show the consistent picture of a missing influence of size on survival in isolated PM: Konstantinidis et al. [143] N = 20, n. s. (p = 0.78); Tosoian et al. [183] N = 42, n. s. (p = 0.602); Reddy et al. [259], n. s. (p = 0.17). This result is further confirmed in a 10-year literature review that also found no relationship between metastases size and SR (Dong et al. [194] N = 95, n. s. (p = 0.87). In publications that also included individual PM with simultaneously resected extrapancreatic metastases in their collectives, there are consistent results: Schwarz et al. [181] N = 62, n. s. (p = 0.93); Di Franco et al. [232] N = 21, n. s. (p = 0.569); Milanetto et al. [235] N = 39, n. s.

(p = 0.80); Blanco-Fernándes et al. [243] N = 116, n. s. (p = 0.81). In summary, even for the parameter "size of metastases", the communications presented do not show any significant impact on the OCTs.

3.3. Risk Factors Related to the Time of PM Operation

3.3.1. Synchronous Versus Metachronous Occurrence

Detailed information on these factors was provided in 453 casuistic communications. The result of the meta-analysis is shown in Figure 4 with a cumulative five-year SR of 64.9% and 75.7%, respectively. The difference is not statistically significant (p = 0.757). Large single and multicentre reports on isPMRCC also found no dependence of survival time on synchronous or metachronous metastases: Tosoian et al. [183] N = 42, n. s. (p = 0.509); Malleo et al. [245] N = 69, n. s. (p = 0.55); Reddy et al. [259] N = 21, n. s. (p = 0.98).

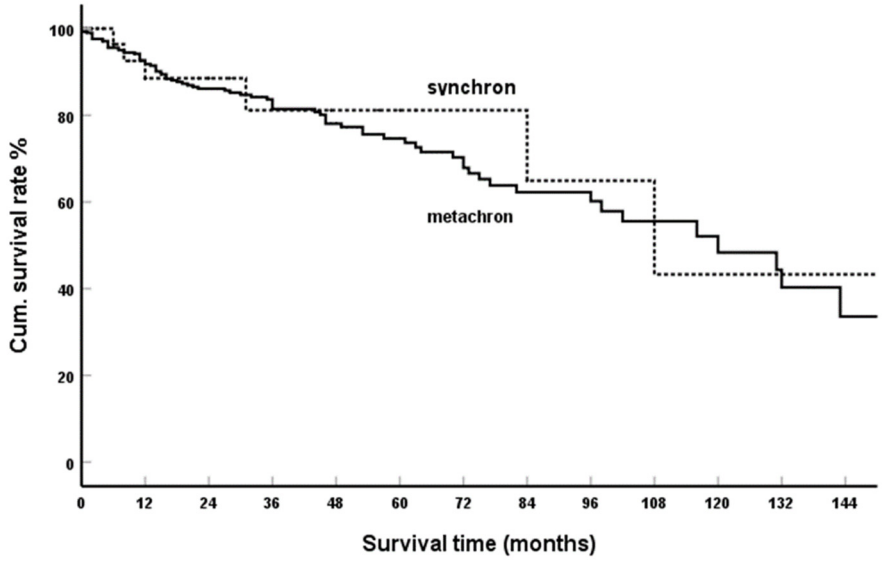

Figure 4. Synchronous vs. metachronous isPMRCC; Kaplan-Meier survival curves (p = 0.757).

In the publications that included cases of PM with synchronously resected extrapancreatic metastases as well, the following results were found in the literature: Milanetto et al. [235] N = 29, p < 0. 001; Blanco-Fernandes et al. [243] N = 116, n. s. (p = 0.45). Results from literature compilations are similar: Dong et al. [194] N = 199, n. s. (p = 0.91); Masetti et al. [144] N = 187, n. s. (p = 0.092); Tanis et al. [137] N = 293, n. s. (p = 0.509). Thus, in summary, the results in isolated PM, both the casuistic and the single and multicenter reports, provide the consistent result of a lack of influence of synchronous vs. metachronous progression on survival. This uniform picture of isolated PM is contrasted with the result when observations with extrapancreatic metastases are included in the analyses, while one author also documented a lack of influence [243], the other saw a dependence of SR on synchronous or metachronous occurrence [235].

3.3.2. Interval between Nephrectomy and PM Diagnosis

No relevance between interval and survival can be documented from 420 sufficiently documented case reports: HR 1.004; 95% IV 0971–1.038; p = 0.830. For isolated PM, the only major single institutional report published so far confirmed this result: Tosoian et al. [183] N = 42, n. s. (p = 0.738) as well as a 10-year literature review: Dong et al. [194], N = 199, n. s. (p = 0.53). Reports that include both isolated PM and PM with synchronously resected extrapancreatic metastases are available in at least four large single and multicentre reports: Schwarz et al. [181] N = 62, n. s. (p = 0.73); Di Franco et al. [232] N = 21, n. s. (p = 0.143); Milanetto et al. [235] N = 33, n. s. (p = 0.96); Blanco-Fernándes et al. [243] N = 116, p = 0.03. In summary, the studies on the influence of the interval show that as long as only isolated PM are considered, there is no evidence of a dependence between interval and OS. Only

when PM observations with extrapancreatic metastass are included does this homogeneous picture change; in at least one of four studies a significant influence occurs now [243].

3.4. Extent of Resection

The comparison between standard resections (N = 394) and local resections (N = 36) is shown in Figure 5. The cumulative five-year SR was 74.8% vs. 80.4% (p = 0.252). In the only reported high volume publication of isolated PM analysing these data, the lack of effect of extend of resection is confirmed: Malleo et al. [245] N = 69, n. s. (p = 0.61), as well as in a literature review by Dong et al. [194] N = 151, n. s. (p = 0.94). The same is true for the only work in this field, which includes cases with synchronously resected extrapancreatic metastases: Milanetto et al. [235] N = 36, n. s. (p = 0.43).

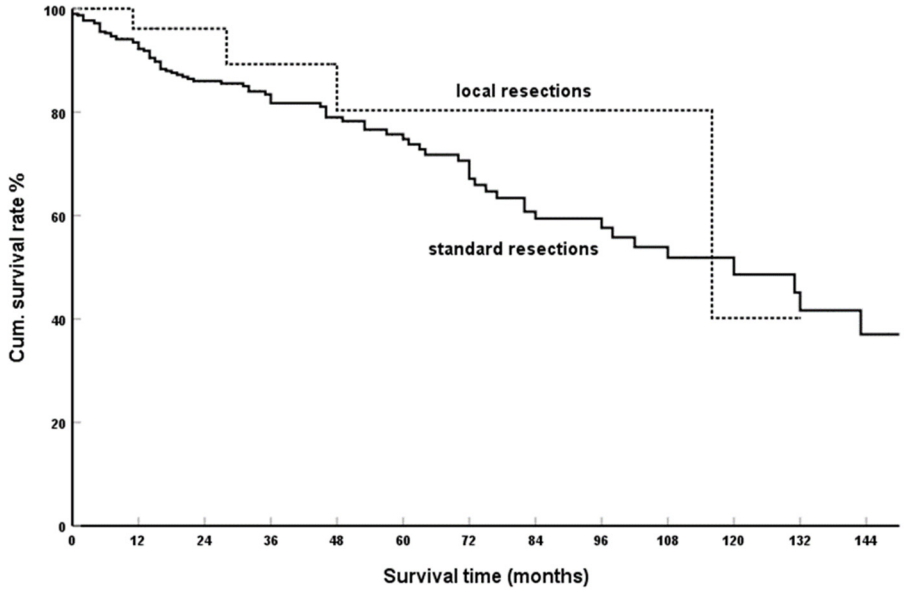

Figure 5. Standard vs. local resections in isPMRCC; Kaplan-Meier survival curves (p = 0.252).

4. Discussion

4.1. Genetics/Epigenetics of isPMRCC

Both the spontaneous course and even more pronounced results after curative procedures with isPMRCC show unusually favourable results (spontaneous course: 3-years SR 55%; surgical therapy 5- and 10-year SR 74.8% and 48.4%, respectively). The isPMRCC thus unquestionably belongs to the disease course occurring in 20% of the mRCC cases with low tumour cell aggressiveness and protracted clinical course [131,152,174,180,193,260]. However, not only isolated PM of the RCC is characterized by a protracted course with a favourable prognosis. Additionally, in multiple organ site metastases of the RCC, the presence of PM signals a more favourable course, as Grassi et al. [261] pointed out for the first time and as confirmed by several studies [238,262–267],. Whether the favourable results in isolated PM and in PM in the course of generalization stages are based on the same pathomechanism in different degrees of severity is currently unclear. It is at least conceivable that, in the isPMRCC cases, a second mechanism is added, which triggers SSM and the particularly favourable course (see 4.3).

Several genetic/epigenetic causes that are effective in the occurrence of PM in RCC have been at least partially deciphered in recent years. Already in 2013, the genome of the clear cell RCC was identified [268], which is characterized by the absence or mutation of the VHL tumour suppressor gene (localized at 3p25) and frequent inactivation of the chromatin-modifying genes PBRM1, BAP1 and SETD2 [269,270]. Whereas the occurrence of PAB1 mutations is associated with a poorer prognosis, BPRM1 mutations seem to be associated with a more favourable course [271]. Additionally, according to Voss et al. [272], PAB1 mutations are associated with a reduced prognosis (p = 0.0008), as is the absence of

BPRM1 alterations ($p = 0.0035$). Turajlic et al. [273] investigated the genetic changes that control the metastasis potential of RCC and found three characteristic changes: 1. The loss of 9p21.3 and less markedly of 14q31.2 are specific changes at the beginning of the metastatic process; 2. the metastasis potential of RCC is reduced by low intratumoural heterogeneity and small proportion of somatic copy-number alterations; and 3. distinct patterns of metastasis are caused by punctual branches evolution. The authors also present three isPMRCC observations in detail that show a genetic profile different from RCC metastases in other organs: The lack of 9p loss and a significant lower weight genome instability index, which underlines a high genetic stability of these tumour cell clones. Singla et al. [238] finally uncovered, in 2020, the genetic characteristics of PM of the RCC, which occurred either isolated or as part of a multi-organ site metastasing RCC. In PM cell clones, they found changes that were associated with less aggressiveness of the disease, such as low rate of PAB1 (3%) and high rate of BPRM1 alterations (77%). Furthermore, they also found evidence of a relative genetic stability of the tumour cells, as they report that limited diversification is observed in the primary tumours leading to PM but also in the PM themselves and summarize that tumours and metastases from patients with PM are characterized by a limited spectrum of alterations consistent with a constrained evolutionary process. Thus, the occurrence of PM in RCC is linked to genetic changes that are associated with low aggressiveness of the cell clones, such as lack of 9p and 14q loss, low weight genome instability index, low frequency of BAP1 alterations and high frequency of BPRM1 loss.

4.2. IsPMRCC and Risk Factors

Early literature reports advised against radical operations in synchronous or multiple isPMRCC, since a poor prognosis was feared in these cases [81,90,93,161,174]. However, this assumption had to be discarded already with the first major literature collections [106,137] and high volume (N > 20) institutional reports [181,183,184,259], since it was not possible to prove that the OS was dependent on the synchronous or multiple occurrence of PM. This implies that patients with multiple or synchronous PM are as good candidates for surgical therapy as patients with singular or very late PM. Since then, numerous studies have shown that not only synchronous vs. metachronous [137,183,194,235,243,245,259] and single vs. multiple [137,143,181,183,184,194,215,232,235,243,245,259], but also size [143,181,183,194,232,235,243,259] and number [232] of PM, the interval to the occurrence of PM [181,183,194,232,235,243] and the extent of resection: Local vs. standard resections [194,235,245] do not significantly influence the prognosis. In addition to the name-giving peculiarity of isolated PM, there is the additional clinical peculiarity that these risk factors are not effective in isPMRCC. This behaviour fully affects the observations with isolated PM of the RCC, i.e., cases in which metastases occur exclusively in the pancreas. No influence of these risk factors could be identified in all such literature releases. The inclusion of individual observations of PM with synchronously resected extrapancreatic metastases in individual studies may weaken this behaviour; synchronous occurrence [235] and interval [243] was identified as a negative risk factor in at least two such publications. Therefore, according to the results presented here, it cannot be excluded that the latter group is associated with a more unfavourable outcome, even if two individual studies did not observe a significant difference between the two groups [195,229].

Considering isPMRCC alone, however, apart from the specificity of isolated pancreatic infestation, a further specificity is the independence of the prognosis from risk factors, whose validity is well documented for other oncological indications. After metastasectomy of pulmonary RCC metastases, the foremost site of RCC metastases, number and size of the lesions and interval to the occurrence of metastases have been identified in a variety of publications as predictors of outcome [274–278]. The same applies to liver metastases in RCC. Additionally, the size and number of metastases, metachronous occurrence and interval were identified as risk factors [279–282]. This also applies to the metastases of other primary tumours. These risk factors are equally effective in colorectal cancer metastasis

surgery (liver metastases [283–289]; pulmonary metastases [290–293]). Thus, after clinical R0 resection of organ metastases, a large number of studies show that both the overall tumour burden (singular/multiple metastases, size or number of metastases) and growth rate dependent factors (synchronous/metachronous metastases, interval to onset) influence the outcome. It is therefore all the more striking that the isPMRCC entity behaves to the contrary, which needs to be explained. The same applies to the lack of influence of the extent of surgical therapy. The importance of local resection procedures in the therapy of isPMRCC is controversially discussed in the literature. In addition to the effects of the minor surgical trauma (e.g., on immunosurveillance), the lower pancreatic parenchymal loss is mentioned by the proponents [64,135,142,294]. The opponents, in turn, warn against the increased risk of recurrence and the imminent risk of overlooked regional LN metastases and the resulting poorer prognosis [99,181]. The result obtained from the presented meta-analysis, that there is no difference in survival between local and standard resections (see 3.4), is therefore unexpected and also asks for an explanation.

Before discussing the possible causes of this strange behaviour of isPMRCC, it is necessary to point out the principle of action of these risk factors. All of the risk factors discussed have in common that they are ultimately only an expression of the magnitude of the probability that clinically undetectable, occult micrometastases are already present outside the pancreas at the time of surgery, leading later to tumour progression. It is plausible that with increasing tumour burden, the mass of tumour cells increases as does the number of tumour vessels, and thus the risk of tumour vessel infiltration and embolized tumour cells. It is equally plausible that with an early onset of metastases, i.e., a faster tumour growth, there is an increased probability that additional occult metastases are already present at the time of surgery. However, what prevents this mechanism from having an effect on the isPMRCC?

4.3. IsPMRCC and Seed and Soil Mechanism

The definite or at least for a very long time exclusive occurrence of PM in RCC cannot, as initially assumed, be due to the topographic proximity of the kidney and pancreas via pre-existing lymphatic [22,66,79,84,138,154,161,177] or venous renal-portal vascular connections between the kidney and the nearby pancreas [84,295,296] or by acquired pathological tumour vessels of hyper-vascularised tumours [10,22,66,79,84,115,138,153,161,173,205]. As our working group pointed out already in 2018, the local metastasis pathway is not compatible with the following characteristics of the isPMRCC [297]: (1) The independence of the distribution of metastases in the pancreas from the side of the primary RCC [106,143,160,183,184,188,211,233,259,297,298], (2) the even distribution of isolated PM within the pancreas [299], (3) the rare occurrence (6.2% [300]) of regional LNN metastases [99,102,111,116,121,143,162,176,179,181,183,184,186,188,209,211,222,230,232,235,243,251], (4) the observation that of the few cases of extrapancreatic metastases diagnosed and removed between RCC surgery and the onset of PM, 78.3% were unquestionably of systemic haematogenic origin [22,55,62,63,66,81,99,124,131,134,145,155,163,169,187,188,193,205,228,230], (5) with a value of 8% [299] the rate of subsequent liver metastases is 2022 (24/288) not increased [10,64,68,79,80,84,106,118,134,135,154,155,169,180,217,230], and (6) recently reported for the first time the simultaneous occurrence of multiple isolated pancreatic metastases and a metastasis in an ectopic pancreas [254]. These are factors that can only be reconciled with a high importance of a systemic hematogenic metastatic pathway, since only this pathway can produce an even distribution of metastases in the pancreas (points 1, 2, 4 and 6). (Conversely the local tumour cell spread should offer for right sided RCC a greater chance to metastasize in the near caput pancreatis and for left sided RCC in the nearby corpus and cauda pancreatis, thus resulting in a dependence of metastasis localisation from RCC side. However, this is not the case, which confirms a low importance of the local metastatic pathway. The low rate of LN and liver metastases (points 3 and 5) also allows only a minor significance of the local lymphatic and local venous, i.e. direct renal-portal metastatic pathway, since this would have to be associated with an

increased rate of LNN and liver metastases). However, if epidemiological studies suggest that systemic hematogenic metastasis is highly valued in the isPMRCC, this inevitably leads to the next question: Why, despite the systemic hematogenic metastasis pathway, do the metastases occur only in the pancreas? According to current knowledge, this can only be explained by the assumption of a simultaneous selection mechanism—a SSM that allows embolized RCC cells to settle and grow to metastases only in the pancreas [297]. The SSM discovered in 1889 by Paget [301] means that the pattern of metastatic spread of cancer is not random, but that the individual tumour entities are assigned preferred host organs [302]. He aptly called this behaviour "Seed and Soil Mechanism", since successful metastasis formation is the result of a multi-stage, cascade-shaped interaction of cancer cell properties (seed) with those of the host organ (soil). The settlement and growth of an embolized tumour cell to clinical metastasis can and will therefore only take place in an organ in which the respective properties of the host and the tumour cell exactly match each other. Even blocking a single step in this complex process can make metastasis impossible [303–306]. The hypothesis of the existence of an exquisite SSM in isPMRCC [297] is now able to explain all the peculiarities of this entity without compulsion, if the SSM is so exquisitely pronounced that, (a) only the formation of PM is permitted, while (b) all other extrapancreatic embolised renal cancer cells are either definitively destroyed or "arrested" for years and decades in a dormant state [307,308]. The lack of vital extrapancreatic tumour cell nests capable of metastasis formation can now, in addition to the isolated occurrence of PM and the good surgical treatment results, also explain the unconstrained lack of significance of those risk factors, which only reflect the probability of the presence of occult extrapancreatic micrometastases. Since the highly specific and highly effective SSM in isPMRCC causes this probability to tend towards zero in extrapancreatic organs, there are no viable extrapancreatic tumour cell nests and these risk factors must remain ineffective. The lack of efficacy of the mentioned risk factors is therefore not a second independent characteristic of the tumour cells in isPMRCC, but an inevitable consequence of the postulated SSM. The same applies to the interpretation of the non-different treatment results of local and standard resections. As possible explanation for the non-different treatment results of local and standard resections, the hypothesis of the above mentioned SSM must be pointed out again. Since this causes the extrapancreatic absence of viable tumour cells or cells capable of metastasis formation, extensions of the resection boundaries will not lead to an improvement in the results. However, the SSM cannot be solely responsible for the protracted course. It is equally essential for the favourable course that these tumour cell properties remain constant over a period of years and decades. This behaviour has been confirmed by genetic studies which have shown that the occurrence of PM in RCC is associated with cell clones with relatively increased genetic stability [238,273]. So, according to these data, the step-by-step dedifferentiation of the tumour cells with increasing tumour age is unusually low in isPMRCC. This certainly differs from the behaviour more common in malignant tumours, that as the tumour continues to develop (be it primum or metastasis), more and more undifferentiated and aggressive cell clones emerge and prevail, which ultimately determine the fatal clinical course.

4.4. IsPMRCC and Organotropism

The exact cause of this highly specific SSM is (yet) unexplored due to the rarity of the isPMRCC. At present, therefore, only those mechanisms that can trigger organotropism and that have been found in more frequent and better studied tumours can be presented and discussed [299,309–311]. (1) The premetastatic niche (pmN) [302,312,313]. This results from the ability of tumours to "manipulate" a peripheral host organ even before the appearance of metastases in such a way that a special microenvironment is created in it, which enables the formation of metastases by inflammation, immunosuppression, increased angiogenesis, vascular leakiness and extracellular matrix remodelling [306,314–316]. Since the formation of pmN results from an interaction of primary tumour cell derived components (exosomes, microvesicles) [311,312,317–320], tumour mobilised bone marrow derived cells (e.g., MDSC,

TAM) [312,319,321] and the local microenvironment [319,322] this is associated with organotropism. (2) The chemokine receptor–ligand mechanism is a necessary prerequisite for the activation of numerous signal transforming pathways, which are critical in the early metastatic process [323,324]. The chemokine receptors transduce intracellular signals by binding with their homologous ligands, which is crucial for premetastatic recruitment of specific cells e. g. regulatory T cells and tumour colonization [313,324]. Since the chemokine receptor is specific to the tumour cell and the ligand to a host organ, a successful interaction can only take place in organs where the receptor and ligand match exactly, which again triggers an organotropism. This mechanism could be blamed early on for the metastasis behaviour of breast cancer [303]. (3) The metabolic adaptation [310,325]. It is essential for the survival of tumour cells in early avascular metastasis growth, as the supply with energy carriers by diffusion alone is critical. Therefore, those cell clones will gain an advantage in metastasis formation that are able to make the best use of locally available energy sources [310,325–330], by overcoming metabolic barriers by metabolic plasticity, which enables them to use all resources available in an individual organ. Since tumour and host cell properties also have to match in this mechanism, this also leads to organotropism in the development of metastases. (4) Immune-surveillance. An intact immune system is able to recognise tumour cells and combat them as foreign cells. The importance of the immune system in RCC was assumed early on by the extremely rarely observed spontaneous remission of metastases, also in the pancreas [63], which were attributed to changes in the immune defence [331–333]. A dangerous counter-strategy of malignant tumours is therefore their ability to block the immune response. This realization led to the introduction of IT [258,334–336], which tries to restore the immune system and which also proved to be effective in RCC. The result of a study by Singla [238] was therefore surprising: in PM of mRCC, immunotherapy (nivolumab) was ineffective, whereas treatment with angiogenesis inhibitors was highly effective. This observation was matched by the behaviour of the biomarkers determined: while angiogenetic markers were increased, inflammatory markers remained low. This suggests that the occurrence of PM in mRCC is linked to the non-inflammatory subtype [337]. This is characterized by enrichment of endothel cells, low frequency of macrophages, B cells, T cells, NK cells, and neutrophils, marked BPRM1 gene loss, and increased angiogenesis, and thus with a good response to TKI therapy. On the other hand, the lack of inflammatory components explains a non-response to IT [238,338]. This suggests that the tumour cells in this rare tumour entity are recognised and fought by the body's own immune system. Why the immune defence is ineffective in the pancreas alone and leads to organotropism remains unclear.

Limitations of the analysis are its retrospective character and the very long period of investigation (1952–2022). The possibility of bias applies first to casuistic reports in which the indication for surgery is influenced by the individual surgeon and the time of surgery, and for which the chance of publication is greater for unusual courses, be they particularly good, bad or rare, than for "standard" observations. In the case of the large single and multicentre reports, the non-randomized study design, which is retrospective and covers very long periods of time, must also be regarded as a limitation [298], which can cause bias in the case selection. However, these methodological limitations do not seem to have a major impact overall, as the various casuistic, single and multicentre reports produced similar results.

5. Conclusions

In addition to the peculiarity of the exclusive metastasis growth in the pancreas other equal unusual peculiarities of isPMRCC are the ineffectiveness of risk factors associated with the overall tumour burden, the rate of growth and the extend of surgery. All these facts can be explained by the hypothesis of a very exquisite SSM, that allows metastasis growth only in the pancreas, while all extrapancreatic embolised tumour cells are either eliminated or locked into a dormant state. The absence of growth-capable extrapancreatic tumour cells has three effects: (1) Resection of the PM leads to exquisite treatment results,

(2) it explains the independence of the results from the extent of resection (if an R0 situation has been achieved) and (3) it inevitably results in the ineffectiveness of the abovementioned risk factors.

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