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SYSTEMATIC REVIEW AND METANALYSIS OF CLINICAL OUTCOMES AFTER ENUCLEATION OF PANCREATIC METASTASES FROM RENAL CELL CARCINOMA.

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Short Title: Pancreatic metastases from renal carcinoma

ABSTRACT

Introduction: A systematic review and meta analysis of the literature was carried out to determine the clinical and oncological outcome of patients who had enucleation of solitary pancreatic metastases from renal cell carcinoma.

Methods: Operative mortality, postoperative complications, observed survival and disease free survival were analyzed. The clinical outcomes of patients who had enucleation were compared to those of 947 patients collected from the literature who had standard or atypical pancreatic resection for the same disease using propensity score matching

Results: There was no postoperative mortality in the 56 patients who had enucleation of pancreatic metastases from renal cell carcinoma . In 51 patients postoperative complications could be analyzed. Ten patients (10/51=19.6%) had postoperative complications. Three patients (3/51 = 5.9%) had major complications (Clavien-Dindo III or more). Five year observed survival rates and disease free survival for patients with enucleation were 92% and 79% respectively. These results compared favourably with those obtained in patients who had standard resection and other forms of atypical resection (also using propensity score matching). Patients who had partial pancreatic resection (atypical or not) with pancreatic-jejunal anastomosis had increased rates of postoperative complications and local recurrences.

Discussion/Conclusions: Enucleation of pancreatic metastases offers a valid solution in selected patients.

KEY WORDS. KIDNEY CANCER, METASTASES, PANCREATIC METASTASES; ENUCLEATION

INTRODUCTION

Renal cell carcinoma is the most common origin for solitary pancreatic metastases [1] Solitary pancreatic metastases are defined as metastases not correlated to direct invasion by the renal carcinoma without involvement in other organs . Even if uncommon, its prevalence is increasing: several factors may be involved

including diagnosis of renal carcinoma at early stages and longer life expectancy for the patients after the initial diagnosis, more intense follow-up using sophisticated diagnostic techniques, awareness that an isolated pancreatic lesion in a patient who had nephrectomy for cancer might be metastasis from renal carcinoma [2,3]. The continuous improvement and expertise in pancreatic surgery has represented the basis for resection of pancreatic metastases from renal cell carcinoma: such an attitude has been supported by high survival rates after resection. Despite the reported low operative mortality, postoperative complication rates remain high, with prolonged hospital stay, and reduced quality of life, at least in the first years from surgery [4,5]. Controversies exist about the indication to pancreatic resection in patients with metastases from renal cell carcinoma in the era of tyrosine kinase inhibitors [6,7].

Less than half of the patients have symptoms related to the pancreatic metastases, including pain, hemorrhage and jaundice[2,3]. In symptomatic patients, pancreatic resection represents an effective therapeutic approach with both palliative and oncologic efficacy. The analysis of risks and benefits is more difficult in patients with no symptoms or with vague, not specific symptoms. In patients in good general conditions, we may expect a relative long life-expectancy and both standard pancreatic resection or long-term anti-angiogenic therapy may include significant side-effects with reduced quality of life [8,9]. Enucleation and enucleoresection of pancreatic metastases from renal cell carcinoma have been underutilized for the conceptual possibility of recurrent metastases in the remaining pancreatic tissue. Limited pancreatic resection offers the probability of better postoperative quality of life, with reduced surgical trauma, shorter hospital stay, maintaining the endocrine and exocrine pancreatic function. New modern pre- and intra-operative diagnostic techniques, offer the possibility for an accurate definition of the extension and location of pancreatic metastases, preventing the possibility of residual metastatic disease. Limited resections imply also an increased utilization of laparoscopic-robotic surgery, with reduced operative trauma [10,11].

The aim of our study was to review the literature, analyzing the short term and long term clinical outcomes of patients who had enucleation or enucleoresection (wedge resection) of solitary metastases from renal cell carcinoma. We analyzed the occurrence of synchronous and meta chronous metastases From this review we excluded patients who had pancreatic resection for metastases from other types of cancer and patients who had direct invasion of the pancreas by the renal carcinoma.

MATERIAL AND METHODS.

The methods used for the study and inclusion criteria were based on Preferred Reports Items for Systematic Reviews and Meta analyses (PRISMA) (Supplement 1 shows PRISMA Flow diagram) recommendations. A literature search was performed in December 2021, by two investigators who conducted a review of papers reported in PubMed, EMBASE, MEDLINE and Cochrane Database. The strings “pancreatic metastases”, “metastases from renal cell carcinoma” “resection of pancreatic metastases” were used in combination with the Boolean operators “and” “or”. Editorials, letters to the Editor, Chapter in Books, Abstracts in Symposia, were not included in the search. There was no language or time restriction. The registration number at International prospective register of systematic review (PROSPERO) was CRD 42020166225. The study protocol was reviewed by the Ethical Board of the University which determined that Ethical approval and consent were not required as this study was based on publicly available data.

Inclusion and Exclusion Criteria: We included in the study papers which described patients with RCC pancreatic metastasis who had enucleation or enucleoresection of solitary metastases, describing the clinical outcome with

a minimum follow-up of three months. The literature search included papers published from 1978 to December 2021. We excluded patients in which partial pancreatectomy was performed because of direct invasion of the pancreas by the renal carcinoma. From the same center or the same Authors only the most recent paper with the highest number of patients was chosen to avoid duplicate cases. Article related to medical therapy or diagnostic imaging were not considered.

Data Extraction: Data extraction was performed by two reviewers independently; a third reviewer was involved to solve any question in interpreting data. There was no discordance between the two reviewers, so the third review was never involved. The primary outcome was to determine the clinical results of patients who had enucleation or enucleoresection of solitary metastases from renal cell carcinoma (mortality and complications related to surgery, median observed survival and expected observed survival). Secondary outcomes included the prevalence of recurrent pancreatic and extra-pancreatic metastatic disease. Analyzed pre-operative clinical characteristics of the patients were age, gender, symptoms if present, general clinical conditions, co-morbidities, previous metastasectomy, presence of metastases from RCC in other organs.

We tried to define the MSKCC (Memorial Sloan Kettering Cancer Center) score if the MSKCC classification was not defined in the report [8]. A “probable” MSKCC grade (favorable, medium, unfavorable) was assigned on the basis of the information provided. Patients were defined also for the characteristics of the pancreatic metastases (synchronous or metachronous, disease-free interval from the time of nephrectomy, number of lesions and average size, location within the pancreas). Patients were defined for the postoperative clinical outcome (postoperative morbidity and mortality rates, subsequent follow-up, disease-free survival, overall survival, and status at the end of each study). The postoperative morbidity was recorded as a total percentage and based on the presence of significant complications according to the Clavien-Dindo Classification [12]. If the Clavien-Dindo Classification was not mentioned in the reports, grades were assigned based on the information provided. Similarly a pancreatic fistula was defined as Biochemical Leak, Pancreatic fistula B and C according to the International Study Group of Pancreatic Fistula (ISGPF) [13]. Quality Assessment. Two independent reviewers determined the quality and risks of bias of analyzed studies by using the Newcastle-Ottawa scale, and the ROBINS 1 assessment [14]. The Newcastle-Ottawa scale defines the quality of a paper with a score ranging from 0 to 9. Papers with a score greater than 6 were considered of good quality.

Statistical Analysis. Student’s t test and X square test were used where appropriate. Kaplan-Meier curves were used to determine 3 and 5-year observed survival rates and observed recurrence rates. Median survivals were also determined. Comparisons between Kaplan-Meier curves were analyzed by Log-Rank test.

Propensity Score Match Analysis: Patients who had enucleation and enucleoresection were compared to 4 matched groups of patients. The 4 groups consisted each of 30 patients (30 patients who had total pancreatectomy with splenectomy, 30 patients who had distal pancreatectomy with splenectomy, 30 patients who had duodenopancreatectomy, 30 patients who had atypical resection with jejunal anastomosis including middle pancreatectomy and head resection). These 120 patients were randomly selected from 947 patients who had pancreatic resection for metastases from RCC, collected from the literature (378 patients had distal pancreatectomy; 204 total pancreatectomy, 315 duodeno-pancreatectomy and 50 patients atypical resection). We considered several covariates into our model. including: age, sex, general conditions, preoperative symptoms, number of pancreatic metastases, site and size of metastases, interval between nephrectomy and diagnosis of pancreatic metastases, previous metastasectomy in other organs, histology and stage of the previously resected renal carcinoma and tested our model for adequate overlap and covariate balance. For covariate balance, we used the standardized differences after weighting. These were all <0.1, indicating adequate balancing by the propensity score model. We used weighted Cox regression to compare overall survival and overall disease-free survival. Our specific objective was to determine if enucleation and enucleoresection, without splenectomy, lymphadenectomy and without potential risks associated to typical pancreatic resections (diabetes, inflammation related to B-C pancreatic fistula) were correlated with a decreased rate of pancreatic and extrapancreatic recurrences. The hypothesis at the basis of these comparisons was that enucleation and enucleoresection might imply a reduced systemic and local trauma to the immune system and consequent reduced rates of extra pancreatic metastases. To better compare the groups of patients, we selected patients with similar post-operative mortality and complications.

RESULTS.

Literature Search : Six hundred papers published from June 1993 to December 2021, were identified. Two hundred sixty five papers were fully evaluated, but only 33 papers clearly reported patients who underwent enucleation or enucleoresection of pancreatic metastases from renal cell carcinoma (references in Table 1,2,3,4): there were eleven single case reports and 22 papers which described an overall series. Overall 56 patients who had enucleation or enucleoresection were collected , with two patients who had two enucleations in different times. (Table 1, 2, 3, 4).The quality of the papers was good (average 7,5) with a detailed description of the clinical characteristics of the patients in all but 5 patients (Table 4). Follow up after surgery ranged from 4 to 116 months (mean 31.7 months).

Clinical Characteristics of the Patients: Age ranged from 51 to 75 years (mean 65) Out of 51 patients in whom preoperative conditions were clearly described, 44 were asymptomatic, 5 had mild, vague abdominal pain, and only two patients had symptoms related to the pancreatic metastasis (1 jaundice; 1 early satiety and weight loss resolved after surgery). All patients but one were described in general good conditions ("probable" MSKCC grade favorable). In 12 patients the MSKCC score was clearly reported (favorable in all). In all but 6 patients the pancreatic metastases was not associated with synchronous or previous metastases in other organs. Out of the 6 patients with metastases in other organs, one patient had resection of a previous metastasis in the contra-lateral kidney, and five patients had synchronous metastases at the time of pancreatic metastasis diagnosis (2 skin, 2 liver,1 lung), which were all resected. These eight patients were included into the general analysis and their clinical outcome was defined in detail and separately. All but 2 patients have had resection of the primary renal cancer from 1 to 17 years from pancreatic metastasis diagnosis (mean 8.8 years). In two patients the enucleation was synchronous to the nephrectomy.

Characteristics of Resected Metastases. The number of the metastases was clearly reported in 49 cases. The mean diameter of the metastases ranged from 0.6 to 5 cm (mean 1.9 cm). In 38 cases the metastasis was single, in 8 double, in 2 patients there were 3 metastases and 1 patient had 4 metastases. The location of the metastases was clearly reported for 27 patients with single metastases (head in 9 patients, body in 10 patients, tail in 4 patients and involving the head and body in 4 patients) and in 7 patients with two or more metastases (7 head; 4 body; 4 tail)

Type of Surgery.

There were 40 patients who had enucleation or enucleoresection of a single metastasis. Seven of these patients had resection of a recurrent pancreatic metastasis. In all seven patients the recurrent metastasis was located distant from the resection site.

One patient had enucleation of two metastases.

Ten additional patients had multiple pancreatic metastases which implied enucleation and atypical pancreatic resection: 7 patients had two metastases; two patients three metastases and one patient four metastases. Eight of these 10 patients underwent enucleation of a metastasis associated with distal pancreatectomy and two patients underwent enucleation associated with middle pancreatectomy.

In five patients details of the operation were not reported.

Open surgery was performed in all but 5 patients who had laparoscopic resection.

In all patients a final R0 result was achieved. Intra-operative ultrasound examination was performed in more than half of the patients (30/56).

Operative Mortality and Complications: There was no postoperative mortality (0/56). In 51 patients postoperative complications could be analyzed. Ten patients (10/51=19.6%) had postoperative complications. Three patients had major complications (Clavien-Dindo III or more), but only in one patient, who suffered from pancreatitis, the complication was related with the enucleation itself . The second patient suffered from duodenal fistula (the patient had simultaneous duodenal resection) which healed with conservative treatment. The third patient underwent enucleation of a metastasis located in the head and distal pancreatectomy with laceration of the spleen which required splenectomy.

Seven patients suffered from complications, which may be defined minor (Clavien-Dindo I-II), which resolved with conservative treatment : one patient suffered from delayed gastric emptying, and 6 patients (6/51=11.8%) had diagnosis of "small" pancreatic fistula (probably a biochemical leakage in at least 5 of the 6 patients). One of these six patients had wound infection.

Observed Survival . Median survival was not reached (Mean follow-up was 48 months). Four patients died during the follow up with diffuse recurrences respectively at 17, 24, 86 and 116 months. One of these four patients had ,simultaneously to pancreatic enucleation, wedge resection of a liver metastasis; another patient was one of the

only two symptomatic patients (jaundice). Two patients are alive with recurrences respectively at 20 and 96 months. Observed survival was 91.8 (+5)% at 3 and 5 years. After 5 years observed survival was not examined for the small number of patients at risk (8 patients).

Disease-Free Survival The seven patients who had enucleation for recurrent pancreatic metastases were at high risk for a new local recurrence. (4/7= 57%). Not considering into the analysis the latter high risk 7 patients, 3- and 5-year observed disease-free survival for the remaining 44 patients with complete information was 78.6 +-7% and 64.1+-8% respectively. After 5 years observed disease-free survival was not examined for the small number of patients (4 patients) . Nine of the 44 patients suffered from recurrences from 12 to 116 months (mean 33.6 months) from the enucleation or enucleoresection (9/44 =20%) Three patients suffered from pancreatic recurrences: in all patients the recurrence was distant from the previous enucleation, the initial enucleation was R0 and intraoperative ultrasound examination was not performed. The remaining six patients had distant recurrences without pancreatic involvement (Table 1,2,3,4,5).

Propensity Score Matching: Excluding the 7 patients who had enucleation of recurrent pancreatic metastasis, 44 patients with enucleation were compared to 120 matched patients who had standard pancreatic resection for RCC metastases. The match included also similar postoperative mortality and complications rates. Patients who had resection which included a wirsung-jejunostomy had higher distant recurrence rates (21/60= 35% versus 6/44= 14% p=0.04). Distant metastases were diagnosed at an earlier time period after standard or atypical resection which included a Wirsung-jejuno anastomosis (mean 20.2 months versus 33.6 months) (p=0.05). Local recurrence rates were similar in patients with enucleation or with partial typical or atypical pancreatic resections.

DISCUSSION.

Twenty per cent of the RCC patients nephrectomized with intent to cure develop metastases. In a subgroup of patients it takes a long period before metastases are diagnosed [8,9]. Isolated metastases to the pancreas from RCC are rare [49].

The distribution of isolated pancreatic metastases within the pancreas indicates a probable systemic hematogenous spread [1,49]. This is indirectly confirmed by the observation that in 30-40% of the patients metastases in other organs occur within 3 years from resection of isolated pancreatic metastases [8,9,49]. The reasons for the long interval between the diagnosis of solitary pancreatic metastases and the previous nephrectomy are not known. There is the possibility of a slow growing tumor which finds in the pancreas a favorable micro-environment [1]. A comparison between surgical and medical therapy is not possible for several reasons, including the inevitable biases in selection, with patients in better conditions considered candidates for surgery [50]. Reported observed five year survivals for patients who had pancreatic resection for metastases from renal cell carcinoma are around 60% (1,2,3), which are similar with the recently reported results with targeted therapy [51,52,53].

In patients with major symptoms related to the pancreatic involvement (jaundice, bleeding, severe pain) surgery offers palliative and oncologic result.

It is more difficult to define the role of surgery in asymptomatic patients. There is likely to be an important psychological benefit for asymptomatic patients who may not cope with the prospect of no- removal for their metastatic disease.

Sporadic reports testify to an accelerated evidence of metastases in other organs after standard pancreatic resections with splenectomy and removal of not-involved peri-pancreatic lymph nodes [54,55]. In this clinical setting, the possibility of pancreatic fistula (grade B and C) after pancreatco-jejunal anastomosis is high because the pancreas is soft. The consequences of the fistula-related inflammation as well as the possibility of post-resection endocrine and exocrine insufficiency, may lead to reduced immunological response by the patient. New chemotherapeutic agents are able to reduce the growth of metastases from renal cell carcinoma. Clear cell carcinoma is often associated with mutation of the VHL (Von Hippel-Lindau) tumour suppressor gene, which neutralizes the action of hypoxia-inducible factors, involved in the activation of Vascular Endothelial Growth Factor (VEGF) [8,9]. The mutated VHL system is unable to play its normal role, with consequent overproduction of VEGF which stimulated cell growth, micro vessels formation, and tumour aggressiveness [56,57,58]. Basic studies have brought to the development of new antiangiogenic drugs that blocks the action of VEGF and its receptors or mTOR. These drugs have been used successfully in clinical practice. However, these drugs block receptors which are common to other growth factors, with toxic-effects like fatigue, loss of hair, arterial hypertension, liver damage. A decreased immunological response is possible for inactivation also of growth factors involved in

innate (macrophages) and acquired (T cells and other lymphocytes) immunity. Patients may develop resistance to the antiangiogenic drugs [8,9]. Thus, patients should be followed very carefully, and often anti-angiogenic therapy should be modulated according to the response of each single patient, which is variable and unpredictable. In patients with relative long life-expectancy this exhaustive follow-up may not be well accepted by the patients and his/her family.

Limited atypical resection of pancreatic metastases from RCC offers many conceptual advantages: reduced surgical trauma, maintained post-surgical endocrine and exocrine function. The possibility to perform the enucleation laparoscopically reduces further the already low surgical trauma and its consequences.

Underutilization of enucleation has been based on the assumption of high local recurrence rates and on the possibility that pancreatic metastases from RCC are often multiple, even if misdiagnosed [19].

In our review, enucleation was performed in about 5% of the patients. These patients represent a selected group, in good general conditions, often asymptomatic, with limited pancreatic involvement.

The operation compares favourably with standard pancreatic resections, with no mortality and very low complication rates. The possibility of leakage after enucleation of primary pancreatic tumours has been reported to be high, from 30% to 50% of the patients [59,60]. The nature and the growth rate of the primary pancreatic tumour seems to be a major risk factor for pancreatic fistula after enucleation: in cystic tumours pancreatic fistula occurs in more than 50% of the cases, whereas its prevalence is much lower after enucleation of solid tumours (13%)(60). Slow growing pancreatic tumours, like pancreatic metastases from RCC, allow the formation of a compact, multilayered pseudo capsule, which outdistance the tumour from the main pancreatic duct and its major branches. In all studies in which detailed histology was described, the metastasis appeared to be surrounded by a pseudocapsule of fibrous tissue between the tumor and the pancreatic parenchyma. The formation of a pseudocapsule may play a protective role also to contrast the invasion of the metastatic tissue. This aspect is indirectly supported by the fact that all enucleations in the capsular or peri-capsular plane resulted R0.

Thus enucleation can be safely performed remaining in the capsular or in the peri-capsular plane, avoiding injuries to the major pancreatic duct and its major branches and to the parenchymal vessels, still maintaining an oncological efficacy.

In the seven patients who had enucleation or enucleoresection for recurrent pancreatic metastases, local recurrence occurred often (4/7 =57%) and after a short interval (mean 17.5 months- range 12-24). In this clinical setting, enucleation may be rarely indicated.

In our review we found three patients who had local pancreatic recurrence after primary enucleation (3/44 =6.8%) In all patients the recurrence was distant from the previous enucleation, the initial enucleation was R0 and intraoperative ultrasound examination was not performed. From this finding we may hypothesize that the recurrence might have been undetected residual disease, and that intraoperative ultrasound might have helped to prevent the complication.

A major criticism to enucleation is the impossibility to perform a lymph adenectomy more or less extended. The involvement in patients with pancreatic metastases from RCC of the lymphatic system has been reported to be from 0 to 25% [2,3]. Lymph node involvement is more common in patients with symptoms and diffuse pancreatic metastases. In asymptomatic patients with localized metastases lymph node involvement is rare [2,3,17,21,23,34,35,36].

In our propensity score matching comparison we found a higher prevalence of distant recurrences in patients who had standard resections (total pancreatectomy, distal pancreatectomy, duodenopancreatectomy) lymph adenectomy and splenectomy, even if the difference did not reach statistical significance, after a shorter interval from surgery.

However, the hypothesis that a major trauma related to standard pancreatic resections, including splenectomy, removal of uninvolved peripancreatic lymphatics, reduced endocrine and exocrine function may determine a derangement of the immunological response in a clinical scenario of a delicate balance between the host reaction and a slow growing tumour is possible [61,62,63]. At the same time it is conceivable that if the above hypothesis is correct, then there are no viable tumor cell nests outside the pancreas and the additional resection of surrounding structures in standard resections will not lead to better results than enucleations, provided R0 resection is achieved.

CONCLUSIONS. Despite the limitations of our study, we may conclude that enucleation of pancreatic metastases from RCC offers a valid therapeutic solution in selected patients. Laparoscopic-robotic enucleation presents many advantages, and might be an effective solution in asymptomatic patients with localized disease.

LIMITATIONS OF THE STUDY.

The study presents several limitations worth to be mentioned. The review includes a long time period during which diagnostic tests have significantly improved. It is possible that in the past only metastases with a significant size were diagnosed, so that distant or local recurrences were already present and not diagnosed at the time of the pancreatic resection.

There is also a significant bias related with the possibility that patients with isolated pancreatic metastases from RCC candidates to enucleation had less extensive disease which can explain better results and lower prevalence of distant recurrences .

Most studies were retrospective and inevitably data were not complete and not homogenous in the description from centre to centre. The small number of patients operated in different centres relegates any conclusion or assumption to the area of mere hypotheses. Despite these evident limitations our analysis underlines the importance of utilization of less invasive surgery in this clinical setting, considering that improvement in diagnostic techniques will make the prevalence of the disease more common, namely in asymptomatic patients. Less invasive surgery may be an important option in patients who desire to have the metastases removed and not to have the problems related with an exhaustive long term anti-angiogenic therapy.

STATEMENT OF ETHICS

Study approval statement : This study protocol was reviewed and approved by the Council of the Department of Surgery-University of Rome Sapienza.. An ethics statement is not applicable because this study is based exclusively on published literature.

The research complies with the guidelines for human studies and it was conducted ethically in accordance with the World Medical Association Declaration of Helsinki

CONFLICTS OF INTEREST

The Authors have no conflicts of interest to declare

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AUTHORS CONTRIBUTIONS

Antonio Sterpetti conceived the idea and wrote the manuscript

Antonio Sterpetti, Stefania Brozzetti, MariaVittoria Carati collected and analyzed data

Antonio Sterpetti, Stefania Brozzetti, MariaVittoria Carati revised the manuscript and approved final version of the paper.

DATA STATEMENT All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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| Table 1 PATIENTS WITH SIMPLE ENUCLEATION OF PANCREATIC METASTASES AND COMPLETE INFORMATION (n 30) | | | | | | | | | | |
|---|-----------------------|-------------------------------|---------------------------|---|------------------------|--|---|---|-----------------------|---------------------------|
| Authors (year) | Age/sex N pats/ Total | Time from nephrectomy (years) | Symptoms | Number/location pancreatic mets | Size (Max diameter cm) | Operative mortality/ complications | Previous(P)/ Synchronous (S) metastases | Recurrence Location | Disease Free (month) | Survival (month) – Status |
| Sauvanet et al [15](1993) | 64/M 1/2 | 4 | Abdominal pain-Vague | 1/Head | 3.5 | No/No | Skin (S) | No | 18 | 18 Alive Nodisease |
| Hashimoto et al [16](1998) | 62/M 1/4 | 4 | No | 1/Head | 1.5 | No/small fistula | No | No | 13 | 13Alive Nodisease |
| Kassabian et al [17](2000) | 56/M 1/5 | 15 | Early Satiety Weight loss | 1/Head (Wedge) | 5 | No/No | Lung(S) | No | 7 | 7Alive Nodisease |
| Uemura et al [18](2003) | 70/M 1/1 | 17 | No | 1/Body/Partial gastrectomy for gastric cancer | 1.5 | No/No | No | No | 14 | 14Alive Nodisease |
| Bassi et al [19](2003) | ? 1/17 | ? | No | 1/? | ? | No/No | No | No | 33 | 33Alive Nodisease |
| Nakagohri et al[20] (2003) | 71/M 1/1 | 6 | No | 1/Head (Wedge resection) | 1.5 | No/No | No | No | 18 | 18Alive Nodisease |
| Kohler et al [21] (2006) | 65/F 1/5 | 7 | No | 1/Uncinatus Process/Sampling enlarged node (involved) | 3.5 | No/No | No | Yes (Liver, thyroid, maxilla)(all resected) | 16 | 24Alive Nodisease |
| Zerbi et al [22](2008) | 65(mean age) 1/23 | 8(mean) | No | 2/Head and Body | Mean 3 cm | No/small fistula (grade ?) | No | No | Mean 44 | 2-5 years 95-88% |
| Zerbi et al [22](2008) | 65(mean age) 4/23 | 8(mean) | No | 1 /Body | Mean 3 cm | No/ small fistula 1/delayed gastr emptying 1 | No | No | Mean 44 | 2-5 years 95-88% |
| Volk et al [23](2009) | 66/F 1/14 | 14 | No | 1/Head | ? | No/pancreatitis | No | No | 14 | 14Alive Nodisease |
| Volk [23](2009) | 74/M 1/14 | 5 | Jaundice | 1/Head | ? | No/small fistula | No | No local-Diffuse | 116 | 116 Death from disease |
| Akashi et al [24] (2010) | 54/F 1/7 | 3 | No | 1/Head (Wedge) | 1 | No/No | No | Yes local – Pancreatec. | 24 | 44 Alive No disease |
| Gardini et al [25] (2010) | ?/? 1/8 | ? | No | 1/Body | 2 | No/No | No | ? | 18 | 18Alive Nodisease |
| Konstantini dis et al [26](2010) | Mean 68 1/20 | Mean (8.7) | No | 1(?) | ? | No/No(?) | No | No | 4 | 4 Alive Nodisease |
| Konstantini dis et al [26](2010) | Mean 68 1/20 | Mean 8.7 | No | 1(?) | ? | No/No(?) | No | No | 13 | 13 Alive Nodisease |

| | | | | | | | | | | |
|------------------------------|-------------------|-------------|----------------------|-------------------------------------|----------|---------------------|-------------|---|----|----------------------------------|
| Konstantini et al [26](2010) | Mean 68 1/20 | Mean 8.7 | No | 1(?) | ? | No/No(?) | No | No | 47 | 47 Alive Nodisease |
| Chirletti et al [27] (2011) | 70/M 1/1 | 17 | Abdominal pain/Vague | 1/Head (Wedge resection) | 1,8 cm | No/No | No | No | 7 | 7 Alive Nodisease |
| You et al [28](2011) | 54/M 1/11 | 2,7 | No | 1/Body | 0.9 | No/No | No | No | 7 | 7 Alive Nodisease |
| You et al [28](2011) | 51/M 1/11 | 3.5 | No | 1/Head-Body | 1.3 | No/No | No | No | 69 | 69 Alive Nodisease |
| Yazbek et al [29](2012) | 73/M 1/11 | Mean 11.4 | No | 1/Head | Mean 2.3 | No/No | ?/No | Yes local (distant previous resection)+ diffuse.No resection | 12 | 96 Alive With disease |
| Yazbek et al [29] (2012) | 70/M 1/11 | Mean 11.4 | No | 1/Head +Duodenal resection | Mean 2.3 | No/Duodenal fistula | ?/No | No | 60 | 60 Alive Nodisease |
| Yazbek et al [29](2012) | 73/M 1/11 | Mean 11.4 | No | 1/Head (Wedge resection) | Mean 2.3 | No/No | ?/No | Yes pancreas(distant previous resection)- New enucleation (table 4) | 24 | 36 Alive Nodisease |
| Yuasa et al [30](2015) | Mean 66.2 1/13 | Mean 7.8 | No | 1/? | Mean 1.8 | No/No | ?/No | No | 20 | 20 Alive No disease |
| Yuasa et al [30] (2015) | Mean 66.2 1/13 | Mean 7.8 | No | 1/? | Mean 1.8 | No/No | ?/No | No | 20 | 20 Alive No disease |
| Kusnierz et al [31](2015) | 65/F 1/13 | 2 | No | 1/Body/ Wedge resection 1 liver met | 1.5 | No/No | No/Liver(S) | diffuse/No pancreas | 17 | 17 months-Death From disease |
| Wu et al [32] (2016) | 55/M 1/1 | Synchronous | No | 1/Body | 1 | No/No | No/No | Yes 51 months adrenals 84 months lungs | 51 | 86 months -Death from disease |
| Boni et al [33] (2018) | 68/F 1/1 | Synchronous | No | 1/tail | 2.5 | No/No | No/No | No | 9 | 9 Alive Nodisease |

Table 2 2 PATIENTS WITH SIMPLE ENUCLEATION OF PANCREATIC METASTSES AND INCOMPLETE INFORMATION (n 10)

| Author (year) | Total patients | Patients with enucleation | Other types of surgery(%) | Overall Mortality/EnucleationMortality | Overall Morbidity | Overall Disease Free Survival | Overall Observed Survival | Mean Follow up | Recurrences (%)/Mean Interval/Sites | New Pancreatic Resection |
|--|----------------|---------------------------|--|--|-------------------|---|---|----------------|--|--------------------------|
| Schwarz et al (2014) [34] 12 Franco-Belgian Centers | 62 | 4 (6%) | TP 14 (23) PD 19 (31) DP 25 (40) | 4(6.4%)/0% | Not Specified | 3-Year 54% 5-year 35% 10-year 27% | 3-year 72% 5-year 63% 10-year 32% | 91 months | 37 pts (60%) 26 months Pancreatic 9 (Isolated 5- Associated to mets in other organs 4) | 4 pts |
| Untch and Allen (2014)[35] Single Center | 27 | 2 (7%) | Not specified | Not specified/0 | Not specified | Not specified | 3-year 85% 5-year 62% 10-year 30% | 30 months | Not specified | Not specified |
| Benhaim et al (2015)[36] Single Center | 20 | 1 (5%) | TP 3 (15) PD 6 (30) DP 6 (30) MP 5 (20) | 1(5%)/0 | 45% | 3-year 60% 5-year 60% 10-year 20% | 3-year 72% 5-year 62% 10-year 45% | 69 months | 11 pts (55%) Not specified Pancreatic 1 | Not specified |
| Ruckert et al (2016) [37] 2 German Centers | 40 | 3 (7.5%) | TP 3 (7.5) PD 15 (37.5) DP 12 (30) | 3(7.5%)/0 | Not specified | Not specified | 3-year 90% 5-year 75% 10-year 52% | Not specified | Not specified | Not specified |

Table 3- PATIENTS WHO HAD ENUCLEATION OF PANCREATIC METASTASES COMBINED TO OTHER FORM OF SEGMENTAL PANCREATIC RESECTION(N 10)

| Authors (year) (N pts) | Enucleation Number reported Age/sex | Time from nephrectomy (years) | Symptoms | Number/location pancreatic metastases/Associated Operation if any | Size (Max diameter cm) | Operative mortality/ complications | Previous Synchronous mets | Recurrence Location | Disease-Free months | Survival (months) Status |
|------------------------------|-------------------------------------|-------------------------------|------------|---|------------------------|---|---------------------------|-----------------------------|---------------------|------------------------------|
| Motoyama et al[38] (1993) | 67/F 1/1 | 19 | Vague Pain | Two/head and body/ Enu. head met + DP | 2 | No/No | Skin (S) | No | 18 | 18 Alive Nodisease |
| Ishikawa T et al [39](1993) | 69/M 1/1 | 9 | Vague Pain | Two/head and tail /Enu. head met+DP | 1,5 | No/No | No | Contr. kidney | 18 | 20 Alive Nodisease |
| Bassi et al [19] (1998-2003) | 63/M 1/17 | 12 | No | Two/head and tail/ Enu. head +DP | 0.6 | No/Small pancreatic fistula | No | No | 7 | 7Alive Nodisease |
| Sperti et al[40](2003) | 53/F 1/2 | 1 | No | Two/head and body/ Enu. head+middle pancreatectomy | ? | No/No | No | No | 21 | 21Alive Nodisease |
| Zerbi et al[22] (2008) | Mean age 65 1/23 | Mean 8 Years | No | Two/head and tail/ Enu. head +DPS | 1 cm | No/ "Small" pancreatic fistula/Wound Infection | No | No | 44(mean) | 2-5 Year 95%-88% |
| Deguchi et al[41](2009) | 54/M 1/1 | 10 | No | Three/neck, body, tail/ Enu. 2 +middle pancreatetctomy | 3: 1;0.7 | No/No | No | No | 12 | 12Alive Nodisease |
| Strobel et al[42] (2009) | ? 1/31 | ? | ? | Two/head and tail/ Enu. head+DPS | ? | No/No | ? | No | 12 | 12Alive Nodisease |
| Kitasato et al[43] (2010) | 65/F 1/1 | 6 | No | Four/head-body- tail/Enu. 1+DP | 2 cm | No/No | Liver (S) | No | 20 | 20Alive withdisease |
| Yazbek et al[29] (2012) | 74/M 1/11 | Mean 11.4 | No | Two/Head +tail/Enu. 1 and DP | Mean 2.3 | No/Spleen laceration / Splenectomy | ?/No | No | 108 | 108Alive Nodisease |
| Wiltberger et al[44] (2015) | ?/? 1/13 | 10 | No | Three/Head-body-tail/ Enu. 1+ DP | ? | No/No | No/No | Thyroid Lung Resected | 24 | 26 Death Tumor Related |

Table 4 PATIENTS WHO HAD ENUCLEATION FOR RECURRENT PANCREATIC METASTASES (N 7).

| Authors (year) (N pts) | Age/sex N Pats/ Total | Time from nephrectomy (years) | Symptoms | Number/location pancreatic metastases/Associated Operation if any/Previous pancreatic resection | Size (Max diameter cm) | Operative mortality/ complications | Previous(P)/ Synchronous (S) metastases | Recurrence(months) Location/Surgery if any | Disease-Free (mo.) | Survival (months) - Status |
|-----------------------------|-----------------------|-------------------------------|------------|---|------------------------|------------------------------------|---|--|--------------------|----------------------------|
| Assouad et al [45](2008) | 60/M 1/5 | 2 | No | 1 / body/enucleation / Previous DP | 1,0 | No/No | No | Pancreas (12) TotalPancreatectomy Lung(21) Inferior Lobectomy | 12 | 60 Alive No disease |
| Yazbek et al[29] (2012) | 75/M 1/11 | 12 | Vague pain | 1/ tail /enucleation and transverse colectomy /Previous enucleation head | 2.3 | No/No | No | No | 12 | 12 Alive Nodisease |
| Yoshikawa et al [46](2013) | 74/m 1/1 | 21 | No | 1/tail /wedge resection/Previous PD | 2 | No/No | Contralateral Kidney (P) | No | 12 | 12Alive Nodisease |
| Macrì et al [47] (2014) | 65/M 1/1 | 5 | No | 1/body/wedge resection/Previous DP+S | 2 | No/No | No | No | 16 | 16Alive Nodisease |
| Yuasa et al[30] (2015) | ?/? 1/13 | ? | No | 1/head /wedge resection /Previous DP | 2 (mean) | No/No | ?/No | Pancreas | 24 | 24Alive Nodisease |
| Yuasa et al(30) (2015) | ?/? 1/13 | ? | No | 1/head/enucleation/Previous not specified | 2 (mean) | No/No | ?/No | Pancreas (body)/New enucleoresection | 16 | 24Alive Nodisease |
| Ishikawa H et al(48) (2015) | 51/M 1/1 | 1.5 | No | 1 head/wedge resection/ Previous DP | 1.5 | No/No | No/No | Pancreas (body)/ New enucleoresection | 18 | 24Alive Nodisease |

DP Distal Pancreatectomy.

| | SIMPLE ENUCLEORESECTION | ENUCLEATION ASSOCIATED WITH PARTIAL PANCREATECTOMY | ENUCLEATION ASSOCIATED WITH RESECTION OF SYNCHRONOUS OR METACHRONOUS METASTASES | ENUCLEATION FOR RECURRENT PANCREATIC METASTASES |
|---|-------------------------|--|---|---|
| | 27 patients | 10 patients | 6 patients | 7 patients |
| POSTOPERATIVE MORTALITY | 0 | 0 | 0 | 0 |
| POSTOPERATIVE MAJOR COMPLICATIONS | 2 | 1 | 1 | 0 |
| | | | | |
| LOCAL PANCREATIC RECURRENCE | 3 | 0 | 0 | 4 |
| METASTASES IN OTHER ORGANS DURING FOLLOW-UP | 3 | 2 | 2 | 0 |

TABLE 5 CLINICAL OUTCOMES IN PATIENTS WHO HAD ENUCLEORESECTION OF PANCREATIC METASTASES FROM RENAL CELL CARCINOMA (50 patients with detailed follow-up)