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***PANCREATIC METASTASES – DIAGNOSIS AND
SURGICAL TREATMENT***

PhD THESIS SUMMARY

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INTRODUCTION

Pancreatic metastases are rare pathological entities, about 2-5% of malignant pathology of the pancreas. The rarity of this pathology makes it interesting and exciting, both from the perspective of early diagnostic imaging, as well as multidisciplinary therapeutic possibilities aimed at increasing survival and improving quality of life.

In the current context, technological and therapeutic advances allow a longer survival of the population, which in turn is doubled by the increase in the incidence of neoplastic pathology. On the other hand, the increasing addressability of patients to the doctor, as well as the increasingly advanced paraclinical and imaging possibilities, allow an early diagnosis of tumor pathology and its extension. The multidisciplinary approach to metastatic cancer transforms a pathology with a rapidly lethal evolution in the past, into a chronic pathology with the possibility of evolution, the appearance of new metastases with various locations, as well as new possibilities of therapeutic approach. The expansion and use of the oncological arsenal with a positive impact on survival, using as a prototype the metastatic colorectal pathology in various forms: liver metastases, lung metastases, brain metastases, with increasingly better results, invites the extension of this approach to other cancers, as well as rarer metastases, such as pancreatic metastases.

The malignant pathology of the pancreas is dominated by primary neoplasms, especially exocrine neoplasms such as pancreatic adenocarcinoma, either ductal or acinar type, extremely aggressive, with local and distant evolution with the development of multiple visceral metastases, and, to a lesser extent, by primary neuroendocrine neoplasms, with milder evolution.

The recognition of this pathology is important, even if the incidence is very rare, since once diagnosed these pancreatic metastases can benefit from an appropriate oncological treatment according to the tumor stage: advanced systemic disease, oligometastatic disease or isolated pancreatic metastasis. In the case of multiple multivisceral metastases, systemic oncological approach is the treatment of choice. In oligometastatic disease or isolated pancreatic metastases, the therapeutic options are varied, especially local therapies with no or reduced systemic impact, including surgery with complete resection of the metastasis, whenever possible. This type of approach, coupled with complementary oncological treatment, can provide an increase in survival, quality of life, as well as prevent recurrences.

This paper aims to retrospectively analyze patients with pancreatic metastases, either in isolated form or oligometastatic disease, in whom complete surgical resection has been performed. The imaging monitoring approach is evaluated, as well as multidisciplinary oncological therapy, a central role being played by surgery. The various forms of isolated pancreatic resection (standard or limited) or associated with multivisceral resections are studied, with the immediate postoperative evolution, but also in the long term with the development of recurrence. For renal pancreatic metastases, there are studies that show the effectiveness of non-surgical treatments. In the case of non-renal pancreatic metastases, given the rarity of cases, a comparison cannot be made with non-surgical methods. Among the non-renal pancreatic metastases, those with colorectal origin seem to have a better prognosis due to the varied and effective systemic oncological therapies.

This rare pathology, with an even rarer impact in the context of the complete resection surgical approach, is associated with a series of limitations such as: long study time, heterogenous character, various etiologies, variable addressability, retrospective approach to surgically resolved cases and involves a series of difficulties in establishing adequate conclusions as well as establishing protocols. Moreover, the extensive chronological span determines different oncological approaches, including surgical ones, in the context of medical progress, which makes comparative studies even more difficult.

Regarding the origin of these pancreatic metastases, there is a demarcation between a major pathology related to renal pancreatic metastases, having as a prototype renal cell carcinoma in its various histopathological forms, and a heterogeneous minority group with various origins such as gastrointestinal cancers, genital cancers, lung cancer, testicular cancer, thyroid cancer, sarcomas and melanomas. If in the first group, the unique origin, the slow evolution of metastases that occur at intervals of about 10 years from the primary tumor, as well as the isolated character of the metastasis, make them approachable in a relatively standardized landscape, the 2nd group is extremely difficult to quantify given the rarity and heterogeneous origin.

High-performance imaging advances such as computed tomography and magnetic resonance imaging are able to evaluate these patients and stratify them for systemic or local therapeutic oncological approaches. Taking into account a metastatic pathology (stage IV TNM), the PET-CT evaluation is an important and even mandatory tool, providing an overview

of the neoplastic extension and therapeutic strategy of neoplastic patients. An important element in the context of the neoplastic minority of pancreatic metastases is echoendoscopy, capable of biopsy and immunohistopathological examination to allow differentiation from the primary neoplastic pancreatic pathology. It is also important to include in the differential diagnosis the existence of a pancreatic metastasis in all patients diagnosed with pancreatic tumor and a personal history of cancer.

The anatomo-pathological evaluation is essential in all this advanced oncological stage, especially the immunohistochemical examination, capable of reaching the final diagnosis by identifying the primary non-pancreatic origin.

The research topic is important in the context of patients with radically resolved neoplastic pathology, but with possible recurrence (local or distant), by highlighting the need for continuous careful oncological monitoring, sometimes throughout life in order to early diagnose metastases, especially renal metastases, as well as by multidisciplinary oncological evaluation and guiding potential patients with such pathologies to the high volume general surgery services in pancreatic surgery. The surgical experience gained in centers with high volume and experience in malignant abdominal pathology, including pancreatic, provides the premises for simple or complex pancreatic resections, with or without associated vascular or multiorgan resections, with low morbidity and mortality. In this context, surgery represents a first step in the multidisciplinary oncological approach, such patients requiring a postoperative systemic "consolidation" treatment.

PERSONAL CONTRIBUTIONS

WORKING HYPOTHESIS AND GENERAL OBJECTIVES

The hypothesis from which we started is the usefulness of surgery – complete resection of the pancreatic metastasis – in this category of patients. The impact of surgical treatment in the context of the multimodal oncological approach to pancreatic metastases was studied and the consequences on patient survival, morbidity rates and postoperative mortality were observed.

The general objectives were represented by the oncological stratification of these patients with metastatic disease, the indication for surgery, the type of pancreatic resection, the postoperative evolution, the impact on perioperative and distant survival, the occurrence of recurrence (local or distant).

The main disadvantage: few cases with the impossibility of conducting randomized trials, but also studies between various types of local vs. systemic or local therapies (resection vs. ablation).

GENERAL RESEARCH METHODOLOGY

The evaluation of the group of patients with pancreatic metastases was retrospective, the data collection being from the clinical-surgical observation sheets, as well as from the electronic database of the General Surgery Center of the Fundeni Clinical Institute. The collected data were statistically analyzed according to the number and share of patients with pancreatic metastases.

The paper retrospectively evaluates, over a period of over 20 years, patients from a tertiary general surgery center – Fundeni Clinical Institute – with pancreatic tumor isolated or associated with other visceral tumors preceded by a radically resolved cancerous pathology, and in whom the preoperative or (most commonly) postoperative histological/immunohistochemical outcome was pancreatic metastasis. The primary malignant tumor was studied under descriptive, but also therapeutic and histopathological aspects, oncological monitoring, detection of pancreatic

metastasis and time interval (synchronous or metachronous), oncological reevaluation and surgical indication, aspects of surgical technique and secondary postoperative complications, survival and quality of life, occurrence of recurrence and its therapeutic approach.

Considering their etiology and frequency, we found it useful to divide pancreatic metastases into renal and non-renal.

From the beginning, we analyzed on these two groups the impact of surgery on metastatic neoplastic disease, the immediate postoperative evolution and the distant evolution marked by recurrence. The results were finally compared in all aspects related to postoperative evolution, immediate and distant survival, disease recurrence and multidisciplinary oncological approach.

The first study addresses patients with renal pancreatic metastases operated in the General Surgery Center of the Fundeni Clinical Institute and evaluates this experience in terms of oncological surgical indications, the type of pancreatic resection and the results. Elements such as: overall survival and disease-free interval are also evaluated according to various parameters (age, sex, location of renal carcinoma, time interval of occurrence of pancreatic metastasis, symptomatology, location, presence of extrapancreatic disease and type of pancreatic resection).

The second study concerns patients with non-renal pancreatic metastases and evaluates the role of pancreatic resection on this very rare and heterogeneous subgroup.

Starting from colorectal metastatic pathology with various visceral resections (hepatic, pulmonary) and with extension to pancreatic resection, we conducted a third study on a series of three patients operated on in our center, as well as a review of the literature on colorectal pancreatic metastases.

Another important aspect is the differential diagnosis with primary clear cell pancreatic cancer, recorded in 2 patients discovered during the first study. This extremely rare entity requires the exclusion of metastatic pancreatic pathology, especially from renal cell carcinoma.

Finally, we conducted a comparative study between renal and non-renal pancreatic metastases highlighting the effect on survival and quality of life.

RENAL PANCREATIC METASTASES

Introduction

Pancreatic metastases are rare, accounting for 0.5-5% of malignant pathology of the pancreas, with a higher frequency in necropsies up to 12%. Most are secondary to renal carcinoma – 38.4 – 76.3%. Given their rarity, the role of surgery is unclear, especially in the context of modern systemic therapies, as well as the contradictory results of various published studies.

Patients and methods

The patients in the present study were retrospectively evaluated from the observation sheets and the electronic database of the General Surgery Center of the Fundeni Clinical Institute over a period of 24 years, between January 2000 and December 2023.

Results

A total of 20 patients who underwent surgery for renal pancreatic metastases were identified, respectively 6 females (30%) and 14 males (70%). The median age was 65 years, the range being between 50 and 75 years. In the patients' personal pathological history, renal carcinomas required total right nephrectomy in 11 patients (55%) and left total nephrectomy in 9 patients (45%). The histopathological examination showed in all 20 cases the presence of a clear-cell histological variant of renal carcinoma.

Renal pancreatic metastases were synchronous in 5 patients (25%), most of them being metachronous in 15 patients (75%). The median time to metachronous pancreatic metastases was 8.66 years (104 months) (range 0.5 to 24 years (6 to 288 months)). Two patients developed pancreatic metastases at 23 years post-nephrectomy.

Nine patients were asymptomatic (45%), being diagnosed during careful oncological monitoring. The other 11 patients (55%) had various symptoms such as: upper quadrants abdominal pain - 6 patients (30%), obstructive jaundice - 3 patients (14%), moderate acute

pancreatitis one patient (5%). Two patients (10%) experienced massive upper gastrointestinal bleeding requiring emergency resection.

Computed tomography revealed pancreatic tumors with hypervascular character in arterial time, either single or multiple with diverse location in the head, body or tail, as well as extrapancreatic (liver).

Renal pancreatic metastasis was localized in the head of the pancreas in 7 patients (35%) and in the body/body-tail in 12 patients (60%); One patient had a metastasis to the head and pancreatic body (5%). Pancreatic metastasis was solitary in 16 cases (80%) and multiple in 4 cases (20%). Eight patients (40%) had oligometastatic disease due to the presence of liver metastases in 6 cases (30%) and peritoneal in 2 cases (10%).

Eighteen (90%) patients underwent elective surgeries, only 2 patients (10%) required emergency pancreatic resection for massive upper gastrointestinal hemorrhage unresponsive to radiological embolization or endoscopic hemostasis treatment.

Surgeries consisted of pancreatic resection in 19 cases (17 elective cases), except for a single patient who required palliative biliodigestive anastomosis surgery in a patient with obstructive jaundice due to pancreatic head tumor with multiple liver metastases, who could not be endoscopically stented.

The 19 pancreatic resections for renal pancreatic metastases consisted of: distal pancreatectomies in 11 cases (58%), pancreaticoduodenectomies in 5 cases (26%), total pancreaticoduodenectomy in 2 cases (10%) and enucleation in one case (5%).

Of the 19 patients who underwent pancreatic resections, 14 (74%) had a favorable postoperative outcome.

For elective pancreatic resections, the overall and severe morbidity and mortality rates were 24%, 12%, and 0%, respectively.

The patient with palliative bilio-digestive anastomosis for obstructive jaundice (without pancreatic resection) died 3 months after surgery due to advanced oncological disease.

Of the 17 patients with elective pancreatectomy (metachronous pancreatic metastases) and negative oncological safety limit, 5 had recurrence (30%) at variable time intervals ranging from 2 to 57 months. There has also been one case of recurrence in the case of synchronous pancreatic metastasis in the form of peritoneal carcinomatosis. Recurrence after metachronous pancreatic metastases was with pancreatic localization in 2 patients (12%), hepatic localization in 2 patients

(12%) and a concomitant pancreas-liver localization in one patient (6%). Iterative pancreatic resection was possible in only one patient with strictly intrapancreatic recurrence, the rest of the patients being systemically treated.

The median overall survival estimated by the Kaplan-Meier curve for the 17 patients with elective pancreatic resection and negative oncological safety limit was 128 months post-pancreatectomy (time range 9 to 128 months), respectively 283 months post-nephrectomy for renal cell carcinoma (time range 22-408 months). The estimated survival rates at 1, 5, and 10 years were 100%, 82%, and 60% after pancreatectomy for pancreatic metastasis, respectively, 100%, 100%, and 83% after initial nephrectomy for renal cell carcinoma.

Conclusions

Pancreatic resection for pancreatic metastases can be performed safely and should be performed in all surgical candidates in whom complete resection (negative safety margins) is anticipated, especially in metachronous patients, which is associated with increased overall survival intervals and disease-free intervals. Concerning the type of pancreatic surgery, the limited resection should be the first choice, without jeopardizing the oncological safety, but with better pancreatic function.

NON-RENAL PANCREATIC METASTASES

Introduction

Pancreatic metastases are rare tumors representing 2-5% of all pancreatic cancer, most commonly secondary to renal cell carcinoma. The role of pancreatic resection in this subgroup is less clear in the context of a very rare and multi-cause pathology. This study aims to present the experience of a surgical center with a large volume of pancreatic pathology and the role of pancreatic resection in such a pathology.

Patients and methods

Between January 2000 and December 2023, 15 patients underwent pancreatic resections for non-renal pancreatic metastases at the General Surgery Center of the Fundeni Clinical Institute, Bucharest, Romania.

Results

We included 15 patients: 10 females and 5 males, aged between 28 and 71 years, most of them aged between 40 and 60 years.

As for the origin of non-renal pancreatic metastases, it was represented by: colorectal cancer (2 colon cancers and one rectal cancer) - 3 cases, bile duct cancer (2 gallbladder cancers and one proximal main bile duct cancer - Klatskin tumor) - 3 cases, uterine cancer (one carcinoma and one leiomyosarcoma) - 2 cases, retroperitoneal sarcomas (leiomyosarcoma and liposarcoma) - 2 cases, melanomas (uveal and scalp) - 2 cases, ovarian cancer (adenocarcinomas) - 2 cases and one case of pheochromocytoma.

Five metastases were synchronous, the remaining 10 being metachronous and developing at variable intervals ranging from 1 to 27 years, most being between one and 5 years. Of the synchronous ones, 3 were discovered at the time of diagnosis of the primary tumor and were resected together with it, the other 2 were detected 4 months after the diagnosis and radical intervention of the primary tumor. The metastasis discovered at 27 years after the primary tumor was recorded in the case of the patient with pheochromocytoma with multiple recurrences.

Of the 10 patients with metachronous metastases, 8 underwent adjuvant chemotherapy specific to the primary tumor.

Regarding the symptomatology, 9 patients were asymptomatic, the diagnosis of pancreatic metastases being established following careful oncological monitoring. The remaining 6 patients were diagnosed following symptoms such as: non-specific abdominal pain - 3 cases, obstructive jaundice - 2 cases, gastric outlet syndrome - one case, ascites - one case, and hypertension - one case. It should be noted that there were cases in which patients presented multiple symptoms.

Regarding tumor markers, there was only one case of increase in these markers (CEA, CA 19.9), in a patient with previous resected rectal cancer (low anterior resection) who developed a body pancreatic metastasis about 4 months after resection.

The imaging work-up consisted of abdominal-pelvic ultrasound and computed tomography. The tomographic appearance of pancreatic metastases was variable: hypervascular – sarcomas, pheochromocytoma or hypovascular – colorectal cancer or ovarian cancer.

Echoendoscopy with pancreatic tumor biopsy was available in only one patient with melanoma.

The location of non-renal pancreatic metastases was at the head – 9 cases and in the body and tail of the pancreas – 4 cases.

Patients with metachronous pancreatic metastases, as well as those with synchronous but not simultaneous metastases (2 cases with pancreatic metastases 4 months after the resection of the primary tumor) were evaluated by a multidisciplinary oncology committee and considering either the isolated nature of the pancreatic metastasis – 6 cases, or the oligometastatic disease – 4 cases, surgical resection was chosen. without neoadjuvant treatment.

The resection of the metastases was complete, together with the associated extrapancreatic malignant pathology in the case of oligometastatic diseases, either within the same intervention - 3 cases, or in serial interventions - 1 case (patient with uveal melanoma and pancreatic and pulmonary metastases).

Thirteen standard pancreatic resections were performed (9 pancreaticoduodenectomies and 4 distal splenopancreatectomies) and limited resection (2 median pancreatectomies)

Postoperative complications were recorded in 13 patients.

Recurrence of neoplastic disease was recorded in 9 (60%) patients, of whom 7 (46.67%) were diagnosed with metachronous pancreatic metastases. Two patients could be treated surgically; the others being systemically treated.

Eight patients (53.33%) with recurrence died secondary to the evolution of the oncological disease. Of the 3 patients without recurrence, one died from a non-cancerous cause: acute myocardial infarction.

Patient survival was variable, ranging from one month to 209 months, with 3 patients (20%) alive at the time of writing, with no signs of recurrence.

Conclusions

The diagnosis of a non-renal pancreatic metastasis should be considered in any patient with a pancreatic tumor and a personal history of cancer. A thorough and complete preoperative imaging and histological analysis is necessary to differentiate these metastases from primary malignant pathology of the pancreas. The treatment plan of these patients should be multidisciplinary and careful oncological monitoring can increase the rate of early diagnosis and implicitly improve the prognosis. Surgery can be an important tool in oligometastatic or isolated disease and must be adapted to each patient.

COMPARATIVE STUDY BETWEEN RENAL AND NON-RENAL PANCREATIC METASTASES (PROGNOSTIC CRITERIA)

Regarding the origin of pancreatic metastases, a majority is represented by renal cell carcinoma metastases and a heterogeneous group with numerous origins from a multitude of cancers. In this latter group there are a number of cancers with gastrointestinal and genital origins, sarcomas, melanomas, lymphomas. Due to their characteristics, renal pancreatic metastases are different from the non-renal group, being frequently metachronous, isolated, unique and appearing at long intervals, most often more than 10 years, from the moment of diagnosis of the primary tumor. All these translate into a mild and limited behavior and make them feasible for local treatment, the most indicated being the complete resection of the metastasis, also imposed by its heterogeneous character.

On the other hand, metastases from non-renal cancers are frequently associated with other types of visceral metastases that classify them as oligometastatic or extensive disease. In this context, a very rare subgroup of isolated pancreatic metastases or in the form of oligometastatic disease that can benefit from local surgical treatment occurs.

The usefulness of tumor markers is evident in the case of non-renal pancreatic metastases whose primary tumors are associated with them. It is worth mentioning the role of CEA and CA 19.9 in gastrointestinal metastatic pathology, CA 125 in ovarian pathology or AFP in hepatocarcinoma. They cannot make the histopathological diagnosis, but they require high-

performance imaging examinations capable of highlighting the possible recurrences of the neoplastic disease and their treatment.

Frequently, renal metastatic oncological pathology is recorded in elderly patients who have strongly associated diseases. Even in the context of isolated metastasis or oligometastatic disease, the therapeutic decision is dependent on them. For patients who are good candidates for surgical treatment, pancreatic resection is the treatment of choice.

Non-renal pancreatic metastases are found in patients of different age groups, but frequently the multivisceral character limits local treatment, including surgery. For colorectal pathology and malignant melanoma, systemic therapeutic possibilities can reduce the extension of the disease to the level of oligometastatic disease that can benefit from local treatment.

The type of pancreatic resection is not standardized. Standard and limited (non-standard) pancreatic resections can be used equally, the only condition being that of complete resection of the pancreatic metastasis. For standard resections, one benefit is to perform loco-regional lymphodissection, but multiple studies have shown a reduced level of metastasis in these lymph nodes. Moreover, survival rates in most studies are similar.

Postoperative complications after pancreatic resection for metastases overlap with those of surgery for primary oncological pathology in the context of centers with increased experience in pancreatic resection.

Postoperatively, these patients must be reevaluated oncologically and in the most frequent cases adjuvant treatment in various forms is necessary.

Recurrence is common especially in the non-renal subgroup, is multivisceral and frequently treated systemically.

CONCLUSIONS AND PERSONAL CONTRIBUTIONS

Why should we resect pancreatic metastases?

First of all, the idea of resection of a metastasis is based on rich experience in colorectal cancer metastases in various liver, lung, and brain forms. Equally, the experience gained in pancreatic resection is associated with low rates of morbidity and mortality. A better understanding of the behavior of certain types of cancers (kidney, colorectal, melanoma) also contributes to this, which is able to offer the possibility of resection in the context of an isolated

character and the appearance of pancreatic metastasis after a long time. Last but not least, it is worth mentioning the role of experience and progress in the field of imaging and oncology, valuable tools in the diagnosis and treatment of pancreatic metastases. A special role is played by echoendoscopy, capable of deciding the preoperative diagnosis and the therapeutic strategy.

In the case of renal metastases, their isolated characteristics, with slow growth and a long time interval of appearance after resection of renal carcinoma, make them suitable for surgical treatment. This approach is supported by most current oncology guidelines. Pancreatic resection for pancreatic metastases is safe to perform and should be performed in all surgical candidate patients in whom complete resection (negative safety margins) is anticipated, especially in metachronous pancreatic metastases, which is associated with increased overall survival intervals and disease-free intervals. As for the type of pancreatic resection, the limited one should be of first intention, without jeopardizing oncological safety, but with better pancreatic function by preserving the pancreatic parenchyma. According to the current study carried out on the 17 patients with elective pancreatic resections for renal pancreatic metastases, elements associated with better survival were identified such as: history of left renal cell carcinoma, body-tail location, asymptomatic patients and with an interval of more than 2 years since nephrectomy.

For the category of non-renal pancreatic metastases, the rarity and heterogeneous origin do not offer the possibility of sharp conclusions. Their diagnosis is much more difficult and should be considered in any patient with a pancreatic tumor and a history of cancer. Thorough preoperative imaging and histological analysis is able to reach the final diagnosis of pancreatic metastasis and differentiate it from primary malignant pathology of the pancreas. From this analysis derives a number of important characteristics in the treatment plan of these patients. Multidisciplinary oncological evaluation is able to determine the type of therapy. Surgery can be an important tool in the oligometastatic or isolated disease of this category of patients and must be adapted to each patient.

A differential diagnostic problem, especially in the case of pancreatic metastases originating in clear cell renal carcinoma, is primary clear cell pancreatic adenocarcinoma. Immunohistochemical examination determines the diagnosis and guides the therapeutic strategy.

The comparative study between renal and non-renal metastases shows a better prognosis in terms of survival and disease-free interval for the renal category.

The perspectives refer to:

1. the imposition of more rigorous oncology protocols for monitoring and diagnosis, especially in the case of patients with a history of renal cell carcinoma
2. use of new tumor biomarkers / genetic tests capable of stratifying patients at risk of developing metastases, early diagnosis of recurrence and personalization of oncological therapy
3. extensive use of echoendoscopy, capable of slicing the preoperative diagnosis
4. the usefulness of minimally invasive surgical techniques
5. use of limited (non-standard) pancreatic resection types whenever possible
6. comparative studies with other local or systemic therapies

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LIST OF PUBLISHED SCIENTIFIC PAPERS

1. **Matei E**, Ciurea S, Herlea V, Dumitrascu T, Vasilescu C. *Surgery for an Uncommon Pathology: Pancreatic Metastases from Renal Cell Carcinoma-Indications, Type of Pancreatectomy, and Outcomes in a Single-Center Experience*. *Medicine (Kaunas)*. 2024 Dec 17; 60(12):2074. doi:10.3390/medicina60122074. PMID: 39768953; PMCID: PMC11678890.

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2. **Matei E**, Ciurea S, Herlea V, Dorobantu BM, Vasilescu C. *Colorectal Pancreatic Metastases: A Three-Case Series and Literature Review*. *Chirurgia (Bucur)*. 2025 Feb; 120(1):117-124. doi:10.21614/chirurgia.3083. PMID: 40051324.

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3. **Matei E**, Ciurea S, Herlea V, Dorobantu BM, Vasilescu C. *Pancreatic Resection for Non-Renal Pancreatic Metastases - Experience of a Single Surgical Center*. *Chirurgia (Bucur)*. 2025 Apr; 120(2):169-177. doi:10.21614/surgery.3119. PMID: 40367310.

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