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DIAGNOSTIC YIELD OF COMPUTED TOMOGRAPHY GUIDED FINE-NEEDLE ASPIRATION FOR PANCREATIC CANCER

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Abstract Fine-needle aspiration (FNA) for the histological diagnosis of occupying lesions in the pancreas as opposed to tru-cut needle biopsy to obtain tissue for analysis has been associated with a lower incidence of post-procedure complications, with almost immediate recovery and no need for hospital stay. Nevertheless, the question of the diagnostic effectiveness of percutaneous computed axial tomography (CT)-guided FNA in solid pancreatic lesions has been raised. The aim of this study was to confirm the diagnostic effectivity of percutaneous CT-guided FNA in pancreatic space-occupying lesions and to assess short-term complications. All percutaneous CT-guided FNA with real-time monitoring, performed between April 2010 and December 2015, were retrospectively analyzed. In all cases 21-gauge needles were used. All FNA were performed in the presence of a pathologist who immediately stained and reported as adequate for analysis in all cases. The diagnosis was confirmed by histopathological evaluation. Of 54 FNA performed, final histopathological evaluation revealed neoplastic cells compatible with adenocarcinoma in 52 patients (96%) and was negative for neoplastic cells in two patients (4%). The sensitivity was 94%, and the specificity 100%. Post-FNA morbidity was observed in four patients, consisting of epigastric pain in two and abdominal wall hematoma in two other patients. Percutaneous CT-guided FNA of pancreatic space-occupying lesions was found to be a good, minimally invasive and safe method with low morbidity. The presence of the pathologist in the procedure allowed for immediate cytological diagnosis.

Key words: percutaneous, fine-needle aspiration biopsy, pancreatic cancer, minimally invasive

Resumen ***Rendimiento diagnóstico de la aspiración con aguja fina guiada por tomografía computarizada para el cáncer de páncreas***

El uso de la punción-aspiración con aguja fina (PAAF) en el diagnóstico histológico de lesiones ocupantes de páncreas es una alternativa frente al uso de agujas *tru-cut* en la obtención de tejido para su análisis, con una incidencia más baja de complicaciones y una recuperación casi inmediata sin necesidad de internación. El objetivo fue valorar la efectividad diagnóstica de las PAAF de lesiones ocupantes pancreáticas guiadas por tomografía axial computada (TAC) por vía percutánea, y su tasa de complicaciones a corto plazo. Se analizaron de forma retrospectiva todas las PAAF realizadas mediante guía tomográfica por vía percutánea con control en tiempo real, entre abril 2010 y diciembre 2015. Todas las PAAF se realizaron en presencia de un patólogo que inmediatamente tiñó e informó como adecuado para el análisis. La confirmación diagnóstica se hizo con el análisis anatomopatológico diferido. De las 54 PAAF realizadas, el diagnóstico anatomopatológico informó positivo para células neoplásicas compatible con adenocarcinoma en 52 pacientes (96%) y en otros dos (4%) como negativo para células neoplásicas. La sensibilidad del método fue 94% y la especificidad del 100%. Se registraron 4 casos de morbilidad post punción (2 dolores epigástricos y 2 hematomas de pared abdominal). Las punciones percutáneas de lesiones ocupantes pancreáticas guiadas por TC pueden considerarse un buen método diagnóstico mini invasivo, seguro, con una morbilidad post punción baja. La presencia del patólogo en el procedimiento permitió el diagnóstico citológico inmediato.

Palabras clave: percutáneo, punción aspiración con aguja fina, cáncer de páncreas, mini invasivo

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KEY POINTS

- The percutaneous computed tomography-guided fine-needle aspiration of pancreatic lesions is a valid alternative for histological diagnosis. It might have lower morbidity rate than tru cut needle biopsy, associated with an earlier patient recovery. The purpose of our study was to retrospectively confirm the diagnostic effectiveness of percutaneous CT-guided fine-needle aspiration in unresectable solid lesions of the pancreas and to assess the short-term complication rate.
- In our experience, computed tomography-guided fine-needle aspiration is a safe and accurate method for the diagnosis of solid pancreatic lesions. The procedure is associated with a high sensitivity and low morbidity. Close clinical and imaging monitoring is warranted. The choice of one biopsy method over another should be made based on operator preference and equipment availability.

Pancreatic cancer is one of the main causes of cancer-related deaths both in Europe and the United States[1, 2]. Surgical resection is the only potentially curative treatment; however, only 20% of pancreas tumors are localized and amenable to curative surgery. In spite of advances in the multimodal management of pancreatic cancer, surgical treatment remains a crucial element in the therapeutic algorithm for these patients[3]. Currently, 5-year survival rate for pancreatic cancer is 5%. Nevertheless, tumor resection combined with adjuvant therapy increases survival rate to 15-21%[4-8].

Curative intent surgery is not recommended in patients with pancreatic cancer with distant metastasis or involvement of the hepatic artery or superior mesenteric artery. Therefore, imaging-based stratification is necessary to provide information on tumor location and extension. One of the most commonly used imaging studies is the CT scan with intravenous contrast administration according to a protocol tailored for evaluation of the pancreas[9-11].

In potentially resectable tumors, the need for biopsy is controversial. Those in favor recommend biopsy to confirm the presence of pancreatic carcinoma previous to surgical resection in order to prevent unnecessary surgeries and reduce hospital costs[12-14]. Those against, however, suggest surgical exploration when malignancy is suspected to diminish delay to surgery and avoid tumor seeding along the needle tract[15-18].

On the other hand, in patients who have unresectable tumors or those that are not candidates for surgery, histopathological confirmation is needed. The National Comprehensive Cancer Network (NCCN) guidelines for pancreatic adenocarcinoma strongly recommend histological confirmation in all patients with pancreatic cancer previous to non-surgical treatment[19]. In borderline resectable pancreatic cancer, the possibility of neoadjuvant treatment may be considered, and biopsy would also be indicated.

There are different methods to obtain a specimen of pancreatic lesions, including endoscopic ultrasonographic, surgical, and percutaneous (CT- or ultrasound-guided) biopsy.

Surgical biopsies of the pancreas may be performed by a conventional approach (laparotomy) or by laparoscopy (with the disadvantage that tactile sensation of the lesion is lost). The procedure is both diagnostic and stratifying, as peritoneal implants or liver metastasis that cannot be visualized by CT scan (especially lesions in the body or tail) may be identified. Importantly, one of the goals of the management of pancreatic cancer is to avoid unnecessary surgeries[20-21].

CT- or ultrasound-guided biopsies are percutaneous procedures involving the use of a 20-25-gauge (FNA) or 14-19-gauge (core biopsy) needle for the acquisition of pancreatic mass through the abdominal wall.

Endoscopic ultrasound-guided FNA (EUS-FNA) of pancreatic lesions involves the use of an endoscope that is passed down to the stomach or duodenum. Subsequently, a needle is advanced and punctured through the wall of the gastrointestinal tract towards the pancreatic mass. Although EUS-FNA is the technique of choice to biopsy patients with potentially resectable tumors due to its better diagnostic yield, safety, and lower risk of tumor seeding into the peritoneum[22-24], the necessary equipment is not always available at all centers. In addition, the sedation required during the procedure increases hospital costs. Considering these factors, the percutaneous approach can be preferred over the EUS-guided approach for the biopsy of unresectable pancreatic cancer whenever this last one is not available or even to avoid sedation[24].

FNA of solid pancreatic lesions using a percutaneous approach under ultrasonographic or CT guidance is a minimally invasive procedure that may be performed on an outpatient basis without the need for general anesthesia or sedation. Furthermore, the morbidity rate associated with percutaneous FNA is low, while the equipment is less expensive reducing hospital costs. Although ultrasonography is more commonly available than CT scan, and the latter is associated with the risk of radiation, our general surgery team has more experience with percutaneous CT-guided FNA for biopsies of pancreatic lesions.

The purpose of this study was to retrospectively verify the diagnostic effectivity of percutaneous CT-guided FNA in unresectable solid lesions of the pancreas and to assess the short-term complication rate.

Materials and methods

A retrospective analysis of a prospectively maintained database was conducted including demographic data (sex, age, BMI), perioperative and postoperative data. A total of 54 patients underwent percutaneous CT-guided FNA of solid pancreatic tumors at Hospital Británico in Buenos Aires, Argentina, between April 2010 and December 2015. All pancreatic lesions were evaluated by a multi-slice CT scanner (Phillips Diamond Select Brilliance 16-slice CT) and radiation exposure was simi-

lar to standard abdominal CT scans. Inclusion criteria for the study was the suspicion of an unresectable solid lesion of the pancreas. Exclusion criteria were cystic lesions, coagulopathy (INR > 1.5), thrombocytopenia (<50 000 platelets), BMI >30kg/m^2, metastasis, or disease classified as unresectable.

All FNA were performed by one percutaneous specialist surgeon through the anterior abdominal wall with the patient in dorsal decubitus position in the CT scan. Following infiltration with 2% xylocaine, a 21-gauge needle was used for the aspiration after the pancreatic lesion was localized by CT scan. In all cases, post-aspiration CT-scan was performed to rule out bleeding or other possible complications. Patients were subsequently monitored in the outpatient recovery room and discharged when tolerating food and after spontaneous void with adequate pain management. All patients were followed on an outpatient basis at 7 and 30 days post-biopsy when the final cytopathology results were available. Complications were classified according to the Clavien-Dindo into minor (grades I-II) and major (grades III-IV) complications.

Quality and quantity of the sample obtained were evaluated onsite by the pathologist following fixation of the smears in 96% alcohol and staining with toluidine blue. The presence of the pathologist in the procedure allowed for immediate cytological diagnosis. Whenever possible, excess specimen was fixed in formalin embedded in paraffin and stained with hematoxylin/eosin. Representative cytology smears were subsequently stained using the Papanicolaou technique for final diagnosis.

Cytology results were classified into negative for malignancy, positive for malignancy, and insufficient material. The samples were considered to be diagnostic when the histology report was officially endorsed. A result was considered true positive (TP) when the cytological findings were positive for or highly suggestive of malignancy.

A result was considered a true negative (TN) when the cytological findings were negative for malignancy and there were no findings suggestive of malignancy on clinical and imaging follow-up. A result was considered a false negative (FN) if cytological examination was negative for malignancy but findings suggestive of malignancy were observed during clinical and imaging follow-up. A result was considered a false positive (FP) if cytological analysis was reported to be positive for malignancy but no disease progression was observed during follow-up or findings suggested benign disease.

Ethical approval was waived by the local Ethics Comittee of Hospital Británico in Buenos Aires in view of the retrospective nature of the study, and all the procedures being performed were part of the routine care.

Due to the retrospective nature of the study, the Ethics Comittee waived the requirement for written informed consent; however, all patients signed the surgical consent form.

Results

Overall, 54 patients with a mean age of 68 years (range, 41-92 years) of whom 64.8% were male, were included in the study. Mean lesion size was 3.2 cm (1.5-5 cm). In 64.8% the lesions were located in the head and uncinate process of the pancreas, 29.6% in the body, and 5.6% in the tail. Tables 1a and b show the sociodemographic features of the patients (Table 1a) and pancreatic lesion location (Table 1b).

A mean of four FNA were performed in each patient (range, 2-7). The percutaneous approach was direct in 43, transhepatic in nine, and transgastric in two (Table 2).

Overall, 49 samples were defined as TP for malignancy. Two samples were defined as TN for pancreatic cancer after a two-year follow-up with tumor marker monitoring and CT scans.

Three results were considered to be FN for malignancy. In two of these cases, the final diagnosis was made based on liver metastasis on follow-up imaging studies. In both cases, percutaneous biopsy with a tru-cut needle was performed. A histological diagnosis of neuroendocrine tumor and adenocarcinoma of the pancreas was made, respectively. The third case was a clear-cell tumor diagnosed by surgical biopsy. No FP results were observed. Tables 3a and 3b show the diagnostic results.

CT-guided FNA was found to have a sensitivity of 94% and a specificity of 100%.

Regarding post-FNA morbidity, complications were observed in four patients (7.4%). Two of them presented with epigastric pain without elevated pancreatic enzyme levels or significant clinical or imaging findings and two developed abdominal-wall hematomas seven days after the intervention. When analyzing the tumor location, we found that 3 (5.5%) of these patients had a head/uncinated process and 1 (1.8%) a body tumor. Considering the approach, 3 (5.5%) were directly biopsied whereas 1 (1.8%) was by a transhepatic way. All of them were treated on an outpatient basis without the need for invasive procedures. No severe complications occurred. Table a lists length of

TABLE 1a.– *Sociodemographic features*

Features	N = 54
Male sex (%)	64.8%
Mean age in years (range)	68 (41-92)
ASA III (%)	45%
BMI (Kg/m^2)	22.7
Lesion size in cm (range)	3.2 (1.5-5)
Mean number of aspirations (range)	4 (2-7)

ASA III: ASA Physical Status Classification System III; BMI: Body Mass Index

TABLE 1b.– *Pancreatic lesion location distribution*

Location	N = 54
Head/uncinate process	35
Body	16
Tail	3

TABLE 2.– *Type of approach distribution*

Approach	N = 54
Direct	43 (80%)
Transhepatic	9 (16%)
Transgastric	2 (4%)

TABLE 3a.– *Histologically malignant results (True positive)*

Malignant	N = 49 (91%)
Pancreatic adenocarcinoma	46 (85.6%)
Neuroendocrine carcinoma	2 (3.6%)
Lymphoma	1 (1.8%)

TABLE 3b.– *Histologically non-malignant results*

Non-malignant	N = 5 (9%)
Chronic pancreatitis*	2 (3.6%)
Inflammatory changes*	1 (1.8%)
Normal pancreatic tissue*	2 (3.6%)

**These three results were false negatives (FN). The definitive diagnosis was later obtained (see text)*

TABLE 4.– *Post-operative data*

Data	N = 54
Length of hospital stay	0.5 (days)
Post-FNA complications	4 (7.4%)

hospital stay and post-FNA complications and their correlation with the approach used.

Discussion

Currently, the need for and effectivity of preoperative biopsies for pancreatic lesions remains controversial. Consensus exists on the fact that patients with systemic disease or peritoneal metastasis are not candidates for surgical resection. Those with unresectable systemic or advanced disease require histological confirmation before starting palliative treatment[19]. As liver metastasis is easier accessible to biopsy and provides a higher cell yield than primary pancreatic tumor, percutaneous liver biopsies are commonly performed[23]. Similarly, in patients with advanced but potentially resectable local disease a cytological or histological sample is needed to confirm malignancy before undergoing neoadjuvant therapy. Around 20% of pancreas cancers are resectable; therefore, we might say that the remaining 80% are candidates for a biopsy to determine further management.

Preoperative biopsy in patients with potentially resectable tumor is controversial, because of the significant number of non-diagnostic samples and the risk of tumor dissemination through the biopsy tract. Based on these arguments, a biopsy to confirm tumor malignancy would not be mandatory for surgery with a curative intent if the tumor appears to be malignant and resectable on imaging studies[15, 16, 24, 25]. Nevertheless, if a biopsy is decided to be performed, EUS-FNA is the technique of choice in patients with potentially resectable tumors due to its better diagnostic yield, safety, and lower risk of tumor seeding into the peritoneum[22-24].

Percutaneous FNA of the pancreas was first described in 1975[26,27]. The largest series was reported by Di Stasi et al. in a multicenter study[14]. In different studies, accuracy of ultrasound- or CT-guided percutaneous FNA was reported to be between 61% and 98%[15, 27-34]. In our study, accuracy was found to be 96%. Table 5 shows the results of percutaneous FNA in solid lesions of the pancreas published by different studies.

Generally, specificity of percutaneous FNA is reported to be high; however, sensitivity is relatively low because adequate diagnosis does not only depend on the experience of the pathologist, but also on the procurement of an adequate sample. In addition, percutaneous FNA is associated with a high rate of FN, ranging 23 to 100%. Therefore, FN results should be evaluated with caution and close monitoring of the patient is warranted[35].

In case of metastatic disease, the biopsy should preferably be obtained from the extrapancreatic metastasis, as accessibility of the latter is usually better with a higher cytological yield and a complication rate less than or equal to that of a biopsy of the primary pancreatic lesion[36].

Percutaneous FNA of the pancreas is considered to be one of the easiest techniques to perform and is associated with a high sensitivity for the detection of malignant lesions when located in the pancreatic body or tail[37]. Nevertheless, the anterior approach may be complicated by the interposition of the colon, mesenteric vessels, or spleen. Therefore, a posterior or transhepatic approach may facilitate the procedure.

Complication rate for CT-guided FNA is low, ranging from 3 to 6.7%[13, 15, 37-38]. Although in our study occurrence of post-FNA morbidity was low (7.4%), the rate is high compared to previous reports, probably due to the small number of patients included.

Our study has some limitations. Firstly, our analysis was retrospective. Secondly, procedures were performed by only one surgeon at one institution.

In conclusion, CT-guided FNA is a safe and accurate method for the diagnosis of solid pancreatic lesions. The procedure is associated with a high sensitivity and low morbidity and may facilitate the planning of either neoadjuvant or palliative treatment.

Due to the high FN rate and the slightly higher possibility of malignant seeding, EUS guided FNA could be preferred over CT- guided FNA in patients with potentially resectable tumors, when tissue may be the issue[24]. In lesions that are classified as benign, malignancy cannot be definitively ruled out; therefore, close clinical and imaging monitoring is warranted and repeat biopsy should

TABLE 5.– *Comparison of studies reporting ultrasound- or CT-guided percutaneous fine-needle aspiration*

Study	Year	Number of patients	Sensitivity (%)	Specificity (%)	Precision (%)
Di Stasi (14)	1998	510	94	100	95
Tillou (15)	1996	118	84	91	86
Horwhat (28)	2006	43	62	100	72
Erturk (29)	2006	43	95	N.R.	93
Mallery (30)	2002	70	80	100	81
David (31)	1998	115	98	100	98
Linder (32)	1997	334	69	100	75
Lerma (33)	1996	109	73	100	80
Enayati (34)	1996	119	79	100	82
Matsubara (36)	2008	59	86	100	86
Brandt (37)	1993	251	92	100	93
Rodriguez (38)	1992	41	45	100	61
Hospital Británico	2010/15	54	94	100	94
Median (range)		89.5 (41-510)	81 (45-98)	100 (91-100)	84 (61-98)

be considered in patients with unresectable lesions if malignancy is suspected.

The on-site presence of a pathologist at the time of the procedure favors high-quality sample procurement for diagnosis while reducing the number of passes and the rate of false-positive results.

The choice of one biopsy method over another should be made based on operator preference and equipment availability. Randomized studies with a larger number of cases are necessary to confirm these findings and draw more robust and objective conclusions.

Conflicts of interest: Non to declare

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