

# Laparoscopic management of neuroendocrine tumors: state-of-the-art

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**Abstract:** Over recent years, minimally invasive pancreatic resections have increasingly been reported in the literature. Even though pancreatic surgery is still considered a challenge for surgeons due to its technical difficulties and high morbidity, the consolidation of minimally invasive pancreatic surgery has included the treatment of pancreatic neuroendocrine tumors (PNETs). This article presents a systematic review of the literature with regards to the laparoscopic treatment of PNETs in order to assess the safety and feasibility of laparoscopic pancreatic resections.

**Keywords:** Laparoscopic surgery; neuroendocrine tumors; minimally invasive surgery; review

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Pancreatic neuroendocrine tumors (PNETs) are a rare pathology, representing 2% to 4% of all pancreatic tumors (1), with an increasing rate of diagnosis over the last twenty years (2). Even if many medical treatments have been proposed (3-6), surgery plays a key role in the curative treatment of these tumors, requiring different types of surgical approaches depending on tumor location, ranging from atypical to typical pancreatic resections. Recently, the minimally invasive pancreatic approach has been considered superior in terms of intraoperative blood loss, postoperative pain, time to recovery, and length of hospital stay (7-9).

The aim of this article was to perform a systematic review of the literature, in order to evaluate the feasibility and safety of the minimally invasive treatment of PNETs.

## Materials and methods

A systematic search of the literature, restricted to articles in

English, was performed using MEDLINE<sup>®</sup> and PubMed<sup>®</sup> to identify studies published between January 1, 1999 and March 30, 2015, focusing on patients who underwent a laparoscopic resection of PNETs. This review protocol was developed according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The keywords used to perform the bibliographic search were the following: [(“laparoscopy”[MeSH Terms] OR “laparoscopy”[All Fields] OR “laparoscopic”[All Fields]) AND (“neurosecretory systems”[MeSH Terms] OR “neuroendocrine”[All Fields]) AND (“pancreas”[MeSH Terms] OR “pancreas”[All Fields]) AND (“neurosecretory systems”[MeSH Terms] OR (“neurosecretory”[All Fields] AND “systems”[All Fields]) OR “neurosecretory systems”[All Fields] OR “neuroendocrine”[All Fields]) AND (“pancreas”[MeSH Terms] OR “pancreas”[All Fields]) (“laparoscopy”[MeSH Terms] OR “laparoscopy”[All Fields] OR “laparoscopic”[All Fields]) AND (“insulinoma”[MeSH

Terms] OR “insulinoma”[All Fields]) AND (“pancreas”[MeSH Terms] OR “pancreas”[All Fields]).

Only series with more than 20 patients were included in this study to exclude any selection bias and consider the experience of high volume centers. In case of multiple studies originating from the same group, only the one with the largest number of patients was included in the review. All relevant data and articles were analyzed and extracted by two independent observers (Riccardo Memeo, Stefania Roselli) who consensually decided upon the eligibility of articles.

### Inclusion and exclusion criteria

In this review, comparative studies were included in the analysis and data concerning minimally invasive surgery were extracted manually. Studies reporting data on preoperative, intraoperative, postoperative morbidity and mortality, pathological findings, and oncological outcomes were considered for analysis. Minimum and maximum values were noted for each item. Animal studies and clinical studies including less than 20 cases were excluded.

### Results

The literature search identified a total of 281 potentially relevant articles, 12 of which were chosen (10–21). A flowchart of the selected studies is shown in *Figure 1*. In the end, a total of 596 patients were analyzed.

Most series presented in the study were comparative studies (open versus laparoscopic surgery), except for the study by Cienfuegos *et al.* (15) which described a pure laparoscopic series. This comparison allowed to understand and estimate the percentage of patients who were operated on laparoscopically, with a mean value of 50% (range: 8–100%). Insulinoma, gastrinoma, and non-functioning PNETs were indications for surgery. Insulinoma was the most common indication in 66% of cases. The results were summarized in *Table 1*. Operative time ranged from 123.8 to 352 minutes depending on the volume and experience of the center, with a mean value of 212 minutes per procedure. Blood loss was considerably low, with a mean value of 180 mL per procedure (124.8–250 mL). The mean conversion rate was 13.7% (0–41.3%). Difficult dissection was the most common cause of conversion. As for postoperative morbidity, 33% of patients had postoperative complications. Pancreatic fistula was present in 31% of cases, with a majority of grade A pancreatic fistulas. No

mortality was present in the series. The mean duration of hospital stay was 10 days (range: 5–14.4 days). R0 resection was performed in 95% of cases (range: 80.5–100%).

### Discussion

Many studies in the literature have recently confirmed the possibility of performing a safe and feasible minimally invasive treatment of hepatobiliary cancer (22–31). This review confirms the possibility of performing laparoscopic resection for PNETs.

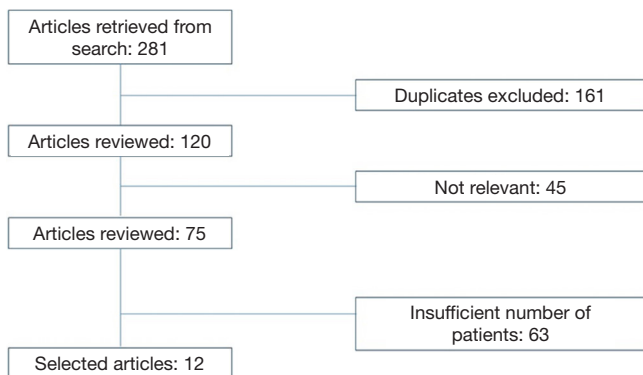
In our review, 12 studies were included in the analysis. Most of them were comparative studies based on open and laparoscopic procedures, and only one represented a series of pure laparoscopic cases. In order to obtain strong data on the subject, series with less than 20 cases were excluded from the analysis. Even if different pathologies were treated in the series (functioning and non-functioning lesions, insulinoma, gastrinoma), patients were included in the review in order to strictly analyze the technical feasibility of the procedure without considering long-term results specific to each pathology. Accordingly, the recurrence rate and oncological results were not considered in the analysis. Given the results of the analysis, operative time and blood loss were comparable to data described in the literature. The conversion rate varies depending on centers. However, the rate of conversion seems reasonable and comparable to previously described data. Conversion was necessary due to difficulties in dissection, and could be considered mandatory in order to perform safe procedures. The morbidity rate varies according to the definition of postoperative complications. The data should be analyzed carefully according to the different classifications provided by authors. The rate of pancreatic fistula was also similar to the data described in the literature for open resections (32), considering that soft pancreatic tissue with a small pancreatic duct seemed to have an increased risk of fistula (33). Given the possibility of atypical resection or enucleation, the rate of fistula could be considered acceptable, as previously described by Drymoussis *et al.* (10). Length of hospital stay, as previously demonstrated in the meta-analysis by Tamburrino *et al.* (32), is considered inferior as compared to open surgery, due to reduced postoperative pain and earlier resumption of food intake.

Our review had several biases. The retrospective characteristic of most studies could well impact the analyzed data. We did not have any detailed information on tumor characteristics and localization and we did not have any

**Table 1** Patients analyzed in the review

Author, type, period	No. of patients	Rate of laparoscopy (%)	Type of PNETs	Type of resection	Operative time (min)	Blood loss (mL)	Conversion (%)	Morbidity, n (%)	Pancreatic fistula, n A/B/C (%)	Mortality n (%)	Hospital stay (days)	RO, n (%)
Drymouisis (R) (10), 1994–2012	203	22%	-	74/64/3: E/DP/O	-	-	-	52/144 (36%)	51/178 (29%)	0	-	-
Xourafas (R) (1), 2004–2014	73	42.7%	NF/Ins/Gas: 64/8/1	51/11/11: DP + S/DP – S/O	352	-	11 (15%)	22 (30.1%)	16 (22%); 12/0/0	0	5	71 (97.3%)
Zhao (R) (12), 1990–2010	46	21.2%	Insulinoma	18/9/19: E/DP – S/O	178.5	124.8	19 (41.3%)	26 (56.5%)	20 (43.5%)	0	15.1	-
Hu (R) (13), 2000–2009	43	48.1%	Insulinoma	21/9/11/2: E/DP + S/DP – S/O	210.5	132.5	2 (4.6%)	13 (30.2%)	9 (20.9%); 2/4/3	0	9.1	-
Han (R) (14), 1995–2016	42	44.7%	NF	42: DP	168.5	175	-	11 (26.2%)	29 (69%); 25/4/0	0	7	42 (100%)
Cienfuegos (R) (15), 2003–2015	36	100%	NF/F: 26/10	1/11/15/9: E/DP + S/DP – S/O	288	-	0	18 (50%)	13 (36.1%); 11/1/1	0	6	29 (80.5%)
Zhang (R) (16), 2010–2017	31	41.9%	Insulinoma/NF: 19/12	16/15: DP + S/DP – S	133.4	200	0	13 (41.9%)	12 (38.7%); 7/4/1	0	14.4	31 (100%)
Song (R) (17), 2005–2013	30	46.2%	-	30: E	123.8	-	-	3 (10.7%)	3 (10.7%)	0	7.8	-
Luo (R) (18), 2000–2007	28	96.5%	Insulinoma	16/1/9/2: E/DP + S/DP – S/O	145	255	2 (7.1%)	5 (17.8%)	4 (14.2%); 0/4/0	0	5.5	-
Roland (R) (19), 1998–2007	22	59.5%	Insulinoma	8/3/7/4: E/DP + S/DP – S/O	318	-	2 (9.1%)	4 (18.2%)	3 (13.6%)	0	13.4	-
España-Gómez (R) (20), 1995–2007	21	61.7%	Insulinoma	9/4/1/7: E/DP + S/DP – S/O	-	211	7 (33%)	16 (76.2%)	10 (47.6%)	0	9.8	-
Zerbi (P) (21), 2004–2007	21	8%	NF/F	-	-	-	-	2 (9.5%)	-	-	-	-

E; enucleation; DP + S, distal pancreatectomy + splenectomy; DP – S, DP – splenectomy; O, other; PNETs, pancreatic neuroendocrine tumors; P, prospective study; R, Review; NF, no functional; F, functional; Ins, insulinoma; Gas, gastrinoma.



**Figure 1** Flowchart of search history (original figure).

sufficient data to understand technical difficulties which had impacted length of stay and conversion rate for instance. No data were provided concerning the type of pancreatic resection. However, different classifications of postoperative complications were integrated into the analysis.

In conclusion, this review demonstrated the feasibility of pancreatic resection for PNETs, with a safe postoperative course and comparable intraoperative results. Future radiochemotherapies (RCTs) are required in order to better identify patients and pathologies which could benefit from this minimally invasive approach for pancreatic lesions.

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## Footnote

*Conflicts of Interest:* P Pessaux is orator for INTEGRA and member of the board of MERCK. The other authors have no conflicts of interest to declare.

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