COMPLEX SURGERY PANCREAS

EVALUATION REPORT

[1/7/2019 – 30/6/2022]

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Belgian Cancer Registry

November 2023

Content

Summary

Introduction

From 1 July 2019 onwards, complex surgical procedures of the pancreas and ampullary region (together referred to as peri-pancreas) were concentrated in 15 acknowledged expert centres that acceded to a convention with the RIZIV-INAMI. The decision to centralize complex pancreatic surgeries in Belgium was supported by volume-outcome results delivered by the Belgian Cancer Registry. These results demonstrated that 30- and 90- day postoperative mortality after complex pancreatic surgery was significantly lower when the surgical procedure was carried out in a high-volume centre.

The aim of the convention is to improve overall quality of care that is delivered in the Belgian hospitals, and in particular to reduce postoperative mortality of complex pancreatic surgeries. All acceded expert centres were subjected to a mandatory registration of each patient that was discussed on a specialized multidisciplinary meeting and every complex surgical procedure that was carried out in the expert centre. A comprehensive evaluation of the centralization project was featured after a three-year period, i.e. based on collected data from 1 July 2019 until 30 June 2022. The results of this evaluation are consolidated in the current report. In addition, some first results for the fourth convention year are introduced.

Results

Volume criteria

An important pillar of the convention, aiming at quality-of-care improvement, was the structural condition of a minimal surgical volume for each individual expert centre. The imposed minimal volume after the three-year period was 75 pancreatic procedures, and was reached by all 15 expert centres. Together with a minimal surgical volume, a minimal volume of specialized multidisciplinary meetings was determined, i.e. 120 discussions after three years. All 15 centres reached the minimal volume of discussions.

Evolution of outcome after complex peri-pancreatic surgery

Data from the Belgian Cancer Registry from the most recent period before the start of centralization, i.e. the four year period 2015-2018, were used as reference ($T0_{2015\text{-}2018}$; N_{T0}=2.261) to compare the results for surgeries that were carried out for primary malignant peri-pancreatic cancer before and after centralization ($N_{3Yconvention}$=1.987).

The ultimate interest is the comparison of the postoperative mortality before and after centralization. The overall unadjusted 30-day postoperative mortality during the $T0_{2015\text{-}2018}$ period was 4.3% 95%CI [3.5, 5.2] compared with the unadjusted result for the three year convention period of 2.6% 95%CI [2.0, 3.4]. When adjusting both results for case-mix characteristics (age group, sex, WHO performance score, type of surgery (pancreaticoduodenectomy versus subtotal pancreas resection)), the adjusted odds ratio for the convention period - with the $T0_{2015\text{-}2018}$ period as the reference - was 0.626 95%CI [0.43-0.91]. Therefore, the observed decreasing trend in the unadjusted overall 30-day postoperative mortality during the convention in comparison to the $T0_{2015\text{-}2018}$ period is proven to be statistically significant (p=0.016). The unadjusted 90-day postoperative mortality during the $T0_{2015\text{-}2018}$ period was

7.3% 95%CI [6.3, 8.4], compared with 5.6% 95%CI [4.7, 6.7] in the convention. The adjusted odds ratio for the convention period was 0.788 95%CI [0.60-1.03], therefore, although a decreasing trend is observed in the 90-day postoperative mortality, the decrease is not statistically significant (p=0.083).

The median time that passed between the histological confirmation of adenocarcinoma and the start of any first treatment (options regarded as first treatment being chemotherapy, radiotherapy or surgery) for the patients treated in T0 was 17 days (IQR 0-30), compared to 19 days (IQR 0-33) for the patients treated in the convention. This slight increase in time to treatment for patients with adenocarcinoma requires attention, analysis could not reveal a difference in time to treatment between patients that were referred and those that presented immediately at the expert centre.

In general, when comparing T0 with the convention, patient selection was comparable as for the age and sex of the patients as well as for the histological subtype and clinical stage of the tumours. During the convention, median age of the patients was 68 years, male-female ratio 1.2. In both periods the largest share of the patients with known clinical stage had tumours stage I or II. An increase in use of neoadjuvant chemotherapy was observed during the convention period (15% compared to 10% in T0).

Evaluation of 15 expert centres

The median age and male-female ratio of the surgically treated patients varied between the different centres, the highest median age being 72 years, and the highest male-female ratio being 2.1. The distribution between adenocarcinoma and neuro-endocrine neoplasms was comparable among all centres, as was patient selection for surgery regarding tumour indication (primary/recurrence/metastasis). The proportion of Whipple surgeries (pancreaticoduodenectomies) varied between the centres from 52% to 83% of all procedures, the proportion of enucleations was similar. Important variation was noted between the individual centres regarding the applied surgical technique, open versus minimally invasive, also the type of minimal invasive surgery varied (laparoscopic versus robotic or hybrid). The median time to treatment for an adenocarcinoma was independent from whether the patient was referred to the expert centre or not, nevertheless 4/15 expert centres had a median time to first treatment of an adenocarcinoma that was at least 5 days longer than to the overall median result of 25 days. The overall 30-day postoperative mortality in patients with benign or malignant peri-pancreatic tumours was 2.4% (95%CI [1.9, 3.1]) (59 deaths over 2.431). As decided by the expert working group, assessment of the centre-specific results was based on statistical significance. The individual results, adjusted for the case mix of the different expert centres, showed a significantly higher 30-day mortality in 2 centres compared with the average. The overall 90-day postoperative mortality in patients with benign or malignant peri-pancreatic tumours was 5.1% (95%CI [4.3, 6.1]) (125 deaths over 2.431), the adjusted results showed a significantly higher 90-day mortality in 1 centre – a different centre from the 2 centres that deviated for the 30-day postoperative mortality - compared with the average, and also a significantly lower 90-day mortality in 2 expert centres compared with the average.

General commitment contributing to a continuous system of quality improvement

All expert centres attended to meetings that were organized by the RIZIV-INAMI to discuss the annual results. The centres also annually prepared an individual evaluation with the

formulation of concrete action points for their own centre. Finally, the 15 expert centres united their scientific interests and created a new scientific group named Belgian Pancreatic Cancer Group (BPCG). The BPCG gathered at regular times to discuss specific surgery-related topics, to exchange experiences and to propose new research questions.

Important obstacles encountered during the convention

The COVID-19 crisis occurred in the middle of the 3-year period, creating diverse supplementary challenges for the expert centres. The possible impact of this healthcare crisis on the individual development and the intended elaboration of the expert centres is an important factor when evaluating the convention.

As for the data collection, collected data on pathological resection margins were susceptible to differences in (interpretation of) the applied guidelines. Likewise, the results regarding the removed lymph nodes were taken cautiously because of suspected differences in the examination method of the resection specimen. Finally, concerns were raised regarding the uniformity of the registration of the postoperative complications.

The different mentioned problems that were encountered each require specific actions in the future.

Other reflective findings

The directives of the convention didn't impose a compulsory discussion of every patient diagnosed with a new peri-pancreatic cancer on a specialized multidisciplinary meeting in an expert centre. A first characterization of the cancer patients that were not discussed on a specialized consult demonstrated that they were on average older and that the stage of their cancer was proportionally more advanced (IV) compared to the patients that were included in the convention. When comparing the unadjusted observed survival 1 year after diagnosis, survival rates for the patients that were not discussed in the convention appeared to be consistently lower than for the patients included in the convention, also when comparing the results by clinical stage. Altogether these observations warrant further investigation and should be considered when evaluating the set-up of the convention and a possible extension to a specialized multidisciplinary consult for every patient with newly diagnosed pancreatic cancer.

First results of four years convention confirm decreasing mortality

With the addition of the fourth convention year, 90-day postoperative mortality was assessed for a total of $N_{4Yconvention}$=2.684, and compared with N_{T0}=2.261. The observed 90-day postoperative mortality for malignant peri-pancreatic cancer during the subsequent convention years evolved from 5.3% (year 1), to 5.8% (year 2), 5.7% (year 3) and 3.7% in year 4. Thereby, the overall unadjusted 90-day postoperative mortality for four years of convention is 5.1% 95%CI [4.3, 6.0], and confirms the decreasing trend.

Conclusion

The evaluation of the first three years of concentration of complex pancreatic surgery in selected expert centres within the context of a convention with the RIZIV-INAMI shows that, notwithstanding the interference of the COVID-19 pandemic, the observed overall 30- and 90-day postoperative mortality decreased in Belgium. The first results of fourth year preserve the decreasing trend. The convention successfully installed a structure of quality control and induced consistent communication between clinical experts. Given the rather short period of evaluation time, continuation of the monitoring of process- and outcome results of the convention is highly recommended.

Abbreviations/definitions

MC expert = multidisciplinary consultation on complex peri-pancreatic pathology organized in expert centre

T0: period between 2015 and 2018

AAPC	Average Annual Percentage Change
AC	Adenocarcinoma
ASA	American Society of Anesthesiologists
BCR	Belgian Cancer Registry
CCI	Charlson Comorbidity Index
CD	Clavien-Dindo
CI	Confidence Interval
IMA	InterMutualistic Agency
INSZ/NISS	Identificatienummer Sociale Zekerheid / Numéro d'Identification de la Sécurité Sociale (Social Security Number)
IQR	Interquartile range
LN	lymph node
M/F	Male/Female
MIS	Minimal Invasieve Surgery
NEN	Neuroendocrine Neoplasm
OD	Odds Ratio
PI	Prediction Interval
RIZIV/INAMI	Rijksinstituut voor Ziekte- en Invaliditeitsverzekering / Institut National d'Assurance Maladie-Invalidité (National Institute for Health and Disability Insurance)
SD	Standard Deviation
WHO	World Health Organisation
WSR	Age-standardised rate

Introduction

1. Background convention complex surgery RIZIV-INAMI

From 1 July 2019 onwards, complex surgical procedures of the pancreas and peri-ampullary region (peri-pancreas) were concentrated in 15 acknowledged expert centres that acceded to a convention with the RIZIV-INAMI (see www.riziv.fgov.be).

CENTRA VOOR COMPLEXE PANCREASCHIRURGIE
CENTRES POUR CHIRURGIE COMPLEXE DU PANCREAS

ERKENNINGS-NUMMER NUMERO D'AGREMENT	CENTRUM VOOR COMPLEXE PANCREASCHIRURGIE CENTRE POUR CHIRURGIE COMPLEXE DU PANCREAS	ADRES ADRESSE	POST POST	GEMEENTE COMMUNE	SAMENWERKING MET [1] COLLABORATION AVEC [1]
710406-22-193	ULB HÔPITAL ERASME	ROUTE DE LENNIK 808	1070	ANDERLECHT	
710403-25-193	CLINIQUES UNIVERSITAIRES SAINT-LUC	AVENUE HIPPOCRATE 10	1200	BRUXELLES	
710099-38-193	GZA ZIEKENHUIZEN – SITE SINT-AUGUSTINUS	OOSTERVELDLAAN 24	2610	WILRIJK	ZIEKENHUIS NETWERK ANTWERPEN
710300-31-193	UZ ANTWERPEN	WILRIJKSTRAAT 10	2650	EDEGEM	AZ KLINA VZW
710689-30-193	IMELDAZIEKENHUIS	IMELDALAAN 9	2820	BONHEIDEN	H.-HART ZIEKENHUIS LIER
710322-09-193	UNIVERSITAIR ZIEKENHUIS LEUVEN	HERESTRAAT 49	3000	LEUVEN	
710243-88-193	JESSA ZIEKENHUIS	STADSOMVAART 20	3500	HASSELT	ZIEKENHUIS OOST-LIMBURG MARIAZIEKENHUIS NOORD-LIMBURG
710152-82-193	C.H.C. – LIEGE	RUE DE HESBAYE 75	4000	LIEGE	C.H.R. VERVIERS CHU-UCL NAMUR – SITE DINANT
710707-12-193	CHU DE LIEGE – SITE SART-TILMAN	AVENUE HIPPOCRATE 15, B 35	4000	LIEGE	
710039-01-193	CHU UCL NAMUR – SITE GODINNE	AVENUE DR. G. THERASSE 1	5530	YVOIR	CLINIQUE SAINT-LUC BOUGE CHU-UCL NAMUR – SITE SAINTE-ELISABETH
710146-88-193	CENTRES HOSPITALIERS JOLIMONT – SITE DE JOLIMONT	RUE FERRER 159	7100	HAINE-SAINT-PAUL	GRAND HOPITAL DE CHARLEROI CENTRE HOSPITALIER DE WALLONIE PICARDE
710049-88-193	AZ ST.-JAN BRUGGE-OOSTENDE – SITE ST.-JAN BRUGGE	RUDDERSHOVE 10	8000	BRUGGE	AZ DELTA
710396-32-193	AZ GROENINGE VZW	PRESIDENT KENNEDYLAAN 4	8500	KORTRIJK	
710670-49-193	UNIVERSITAIR ZIEKENHUIS GENT	CORNEEL HEYMANSLAAN 10	9000	GENT	VZW ALGEMEEN ZIEKENHUIS SINT-LUKAS & VOLKSKLINIEK
710176-58-193	ASZ AALST	MERESTRAAT 80	9300	AALST	

[1] Vanaf 1/1/2020 worden de ingrepen niet meer vergoed in deze ziekenhuizen / A partir du 1/1/2020 les interventions ne seront plus remboursées dans ces hôpitaux

1.1. Why concentrate complex surgical procedures?

Population-based data from the Belgian Cancer Registry (BCR) pointed out that specialized care, in particular complex surgical procedures, can be safeguarded when care is delivered in appropriate circumstances. It was shown that, in the Belgian hospitals, 30- and 90- day postoperative mortality after complex surgery of the pancreas and peri-ampullary region was significantly lower when the surgical procedure was carried out in a high-volume centre *(Appendix B – T0 calculation)*.

1.2. Aim of the convention

The aim of the convention is to improve overall quality of care that is delivered in the Belgian hospitals, and in particular to reduce postoperative mortality of complex pancreatic surgeries *(see Appendix A – convention text)*. Therefore, the convention provides reimbursement of complex surgical procedures of the pancreas and peri-ampullary region carried out for oncological or non-oncological pathology in expert centres. Reimbursement of complex surgical procedures of the pancreas and peri-

ampullary region is to be requested by the expert centres using the following nomenclature codes:

- 242830–242841 Pancreaticoduodenectomy
- 242852–242863 Hemipancreatectomy left with jejunal anastomosis, or approximately total pancreatectomy (95pct)
- 242874–242885 Hemipancreatectomy left
- 242896–242900 Enucleation of pancreatic tumour

1.3. Monitoring of the convention: article 7.6 and 8

All acceded expert centres were monitored by means of detailed registration of each discussed patient and every complex surgical procedure that was carried out in the expert centre. Every centre received annual feedback reports that were created by the BCR and contained an overview of all registered data and quality indicators that were decided by clinical experts and described in article 7.6 of the convention (see www.riziv.fgov.be). Global year reports for the first and second year of the convention, containing data of all expert centres combined, were published by the RIZIV-INAMI. After 3 years the final evaluation of the convention was planned, as described in article 8 of the convention. The BCR was appointed by the RIZIV-INAMI to create the final evaluation report.

1.4. Audit process performed by Audit ziekenhuizen RIZIV-FOD VVVL-FAGG

Independent from the final evaluation report, Audit ziekenhuizen RIZIV-FOD VVVL-FAGG is preparing an individual audit of each acceded expert centre.

1.5. Evaluation/validation by (inter-)national experts

The RIZIV-INAMI invited international experts to review the final evaluation report of the convention *(see Appendix G)*. The national scientific group Belgian Pancreatic Cancer Group was asked to formulate recommendations *(see Appendix H)*.

2. Purpose of this final evaluation report

The final evaluation report is mentioned in article 8 of the convention and aims to answer the following research questions:

- Describe the epidemiology of peri-pancreatic cancer in Belgium
- Compare overall outcome after complex peri-pancreatic surgery before (T0) and during convention-period
- Evaluate the quality of the individual surgical expert centres

3. Information sources consulted for the final evaluation report

To build the final evaluation report, four different data sources were used.

3.1. Complex surgery database

The complex surgery database contains all the data registered at the BCR by the expert centres *(Appendix C – registration form)*. Based on this database the individual feedback reports and the global year reports were created *(Appendix D – global 3-year report, Appendix E – case mix comparisons, Appendix F – centre specific results)*.

3.2. Cancer registration database

The cancer registration database holds information of every new malignancy that is diagnosed in Belgian residents. This database was used to create the T0 calculation for the convention.

3.3. IMA database

The BCR can link the cancer registration database with the administrative database of the InterMutualistic agency (IMA). The IMA database contains information on all medical procedures and pharmaceuticals reimbursed by national health insurance. The IMA database was also used to create the T0 calculation for the convention.

3.4. Crossroadsbank Social Security

The BCR can link the cancer registration database with the database of the Social Security to obtain information on the vital status of the patients.

Remark:

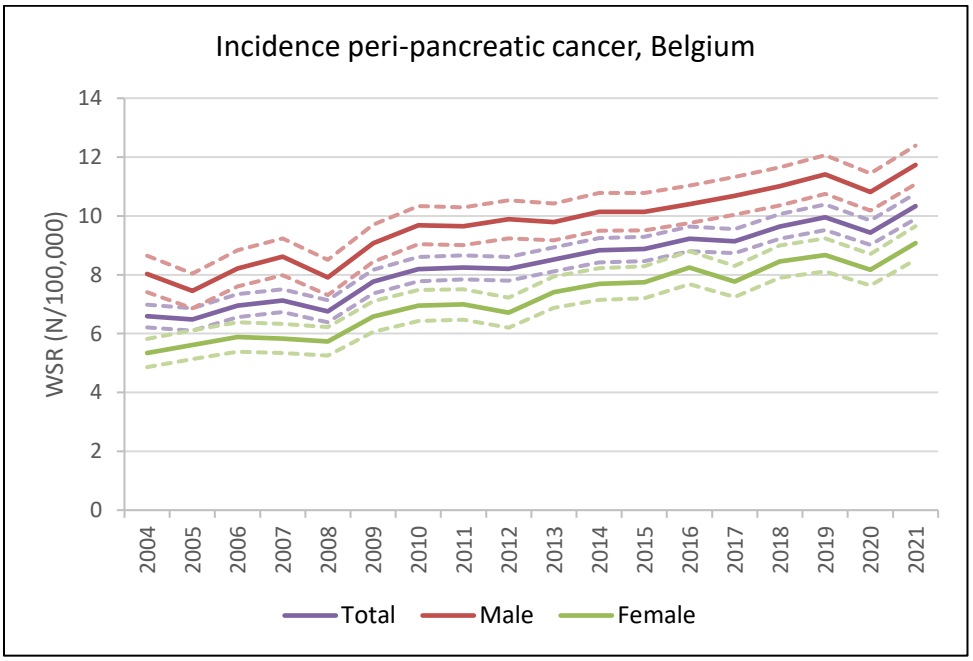
- Note that the T0 calculation published on the website of RIZIV-INAMI *(Appendix B)* applies to the time period 2008-2016, whereas for the comparison of overall outcome after complex peri-pancreatic surgery before (T0) and during convention-period in the current report the time period 2015-2018 will be used for T0. Therefore, results for T0 in this report might differ from the results published in previous reports.
- As decided upon by the RIZIV-INAMI, only patients with official Belgian residence are included in the analyses, foreign patients are not included.
- The pancreas and peri-ampullary region will be named 'peri-pancreas' in this report.
- The COVID-19 pandemic overwhelmed the Belgian health care system starting with its first wave in March 2020. During the convention years (1/7/2019 – 30/6/2022) concerns related to COVID-19 and the possible impact on surgical volumes and outcome after surgery were raised repeatedly by the clinical experts. To evaluate to some extent the impact of the crisis on surgical volumes, the BCR made predictions for the expected surgical volumes during the convention years based on incidence trends of the previous years. Based on these calculations, there was no evidence of a reduced surgical volume on the national scale. However, the BCR was not able to

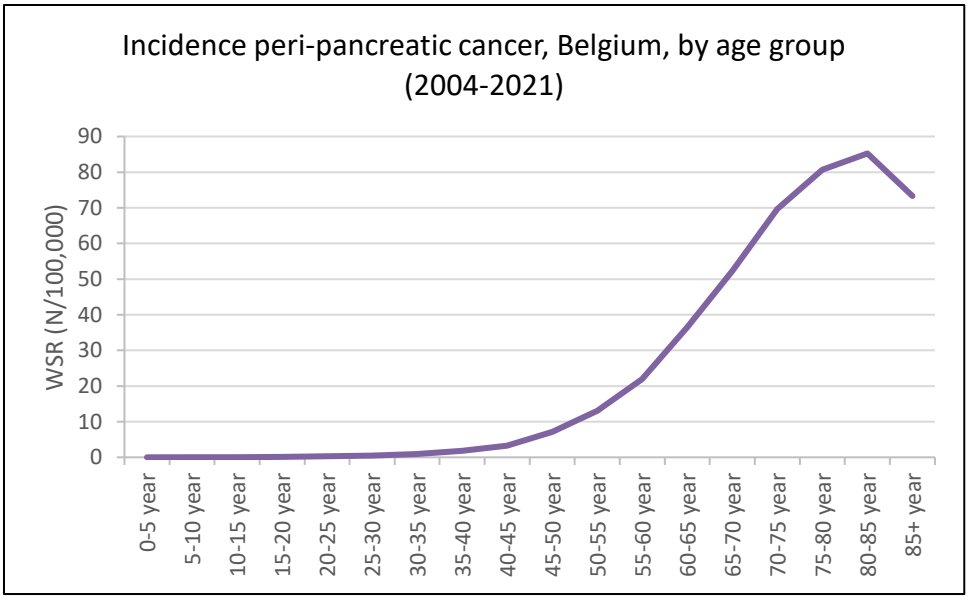
investigate whether there were important regional differences concerning the possible COVID-impact on individual hospital level. Also related to this topic, remarks were made to exclude mortality related to COVID-19 from the results. It was decided that based on international scientific standards, reported mortality should include all possible causes of death.

Epidemiology peri-pancreatic cancer in Belgium

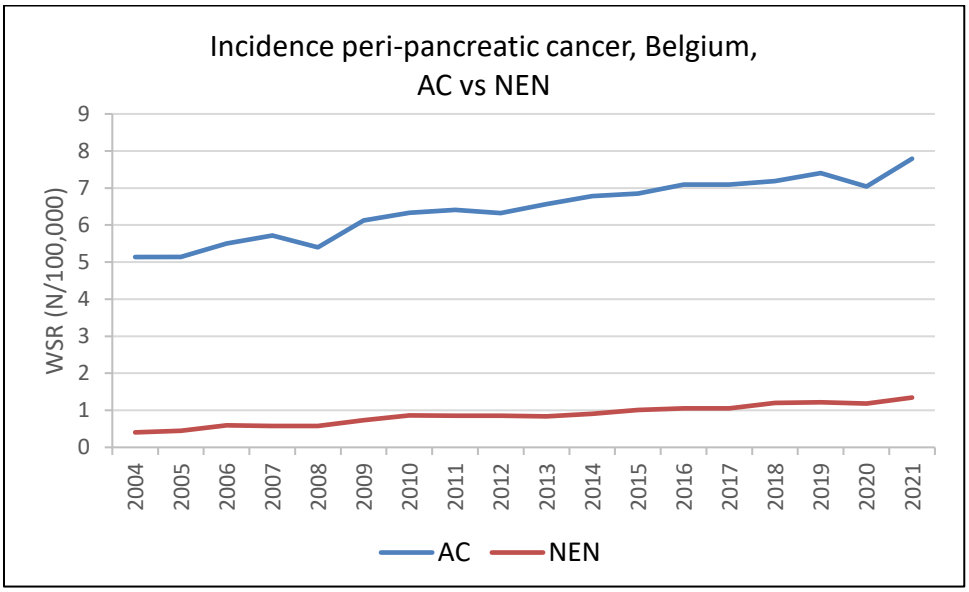
1. Incidence and trend over the years

In 2021, 2754 new diagnoses of peri-pancreatic cancer (including topography of the duodenum, the extra-hepatic bile ducts and the ampulla of Vater) were observed in Belgium, of which 1437 (52%) in males and 1317 (48%) in females. This makes pancreatic cancer the 9th most common cancer in males and the 6th most common in females in Belgium. Pancreatic cancer risk is related with age, a peak in incidence is observed around the age of 80. Between 2004 and 2021, the absolute number of new peri-pancreatic cancer diagnoses increased with 104% (from 1347 to 2754 new diagnoses), corresponding to an increase of 100% in males and 109% in females. This increase is partly explained by the growing and ageing population, however, when we take these elements into account and look at the age-standardized rates (WSR), we see that the overall risk of peri-pancreatic cancer increased between 2004 and 2021 with an overall Average Annual Percentage Change (AAPC) of 2.7 (95% CI [2.3;3.1]; p<0.0001). This increasing risk is noted both in males and in females.

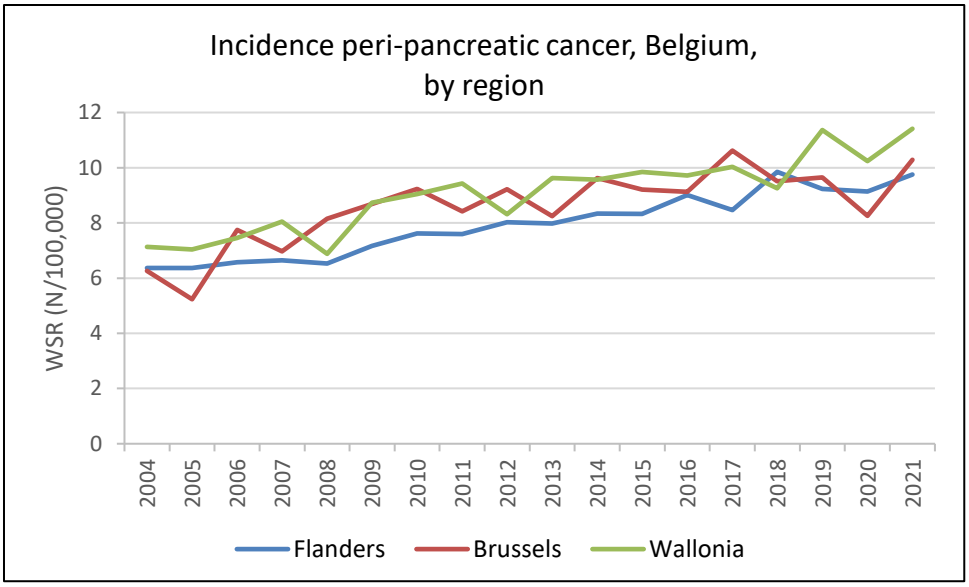




The 2 most common histological subtypes of peri-pancreatic cancer are adenocarcinoma (AC) and neuro-endocrine neoplasms (NEN). In 2021, 2053 new diagnoses of AC and 284 of NEN were observed. Between 2004 and 2021 both the risk of AC and NEN has increased, with an AAPC of 2.3 and 6.9 respectively.



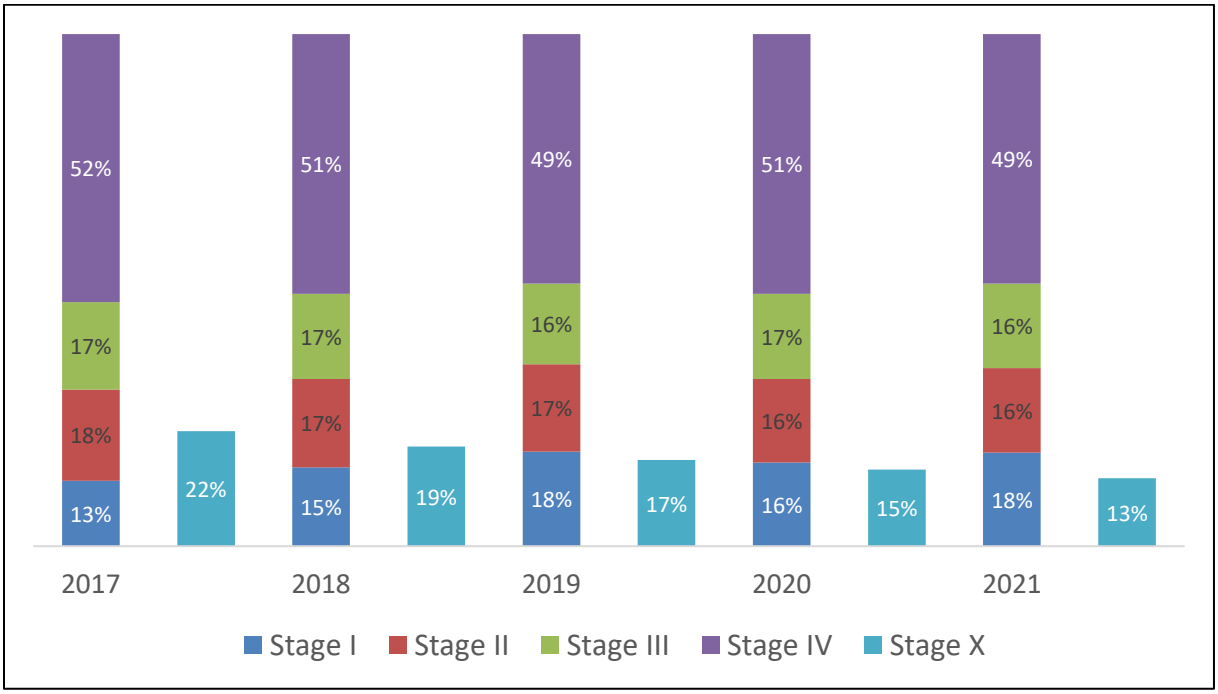
In Belgium, peri-pancreatic cancer risk (WSR) is similar in Flanders and Brussels, and a bit higher in the Walloon region. In 2021, 1617 diagnoses were observed in Flanders (WSR 9.8/100,000), 932 in Wallonia (WSR 11.4/100,000), and 205 in Brussels (WSR 10.3/100,000). The increasing risk between 2004 and 2021 is noted in all three regions at similar rates.



In the year 2020, the COVID-19 pandemic caused a decrease of 6% in overall cancer incidence in Belgium compared to the year 2019.[1] In particular for pancreatic cancer (only topography pancreas) a decrease of 4% was noted in 2020 compared to 2019.

2. Stage at diagnosis

Peri-pancreatic cancer is most often diagnosed in advanced stage. In 2021, 49% of the diagnoses with known stage (pathological stage prevails over clinical unless clinical suspicion of metastasis) were stage IV, 16% stage III, 16% stage II and 18% stage I.



3. Survival and trend over the years

Pancreatic cancer is known for its generally poor prognosis. Most recent CONCORD-survival data (CONCORD-3) report on the period 2010-2014, with 5-year age-standardized net survival rates for pancreatic cancer ranging between 5 and 15% in most countries.[2]

In Belgium, most up to date (period 2016-2021) 5-year relative survival (5yRS) rate of peri-pancreatic cancer is 16.9% (95%CI [16.1; 17.7]). Overall 5yRS in Belgium has improved slightly over the last decades, with 12.7% (95%CI [12.0; 13.5]) in 2004-2009, 14.0% (95%CI [13.3; 14.6]) in 2010-2015, and 16.9% (95%CI [16.1; 17.7]) in 2016-2021.

Survival rates vary substantially according to the stage at diagnosis, 5yRS (2016-2021) for stage I tumours is 53.6%, but decreases to 25.8% in stage II, 17.1% in stage III and 2.3% in stage IV. Also, the histological subtype influences survival, for AC only, 5yRS is 10.4% (95%CI [9.7; 11.2]) versus 72.9% (95%CI [69.5; 76.1]) for NEN only. Finally, survival decreases with the age at diagnosis and survival is better for men (18.1% vs 15.6% for women).

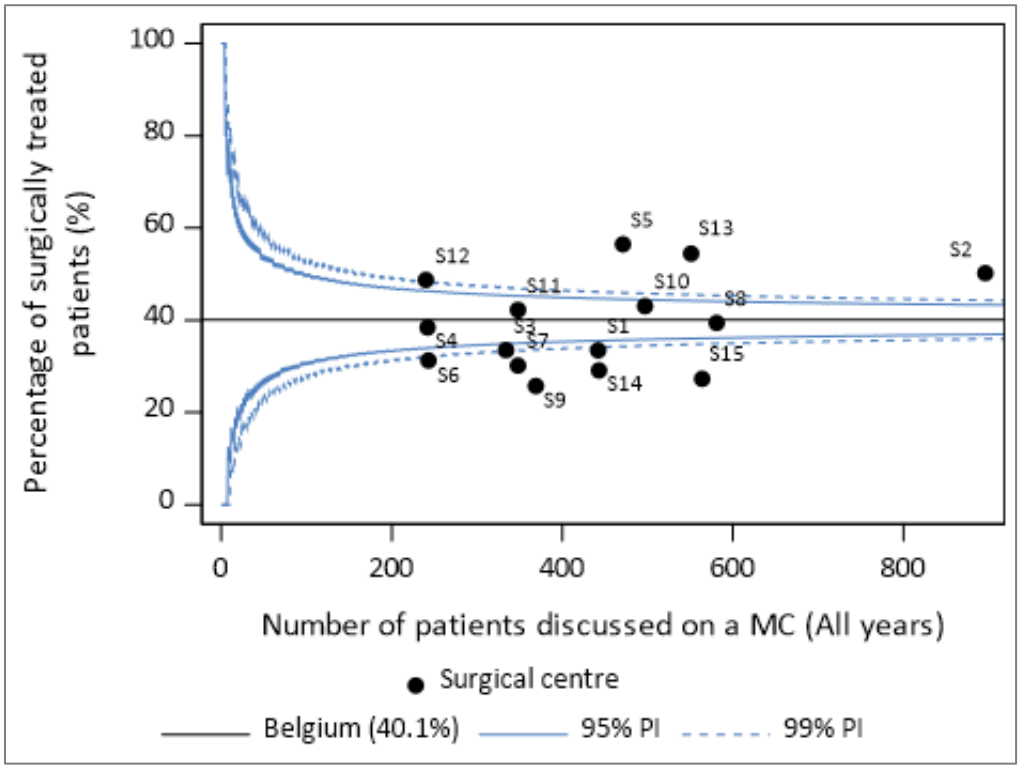
Overview convention data: numbers and volumes

As described in the convention text (article 8), each expert centre is required to achieve a minimal clinical activity after 3 years. This minimal clinical activity is defined as:

- discussion of at least 120 patients on a multidisciplinary consultation for complex (peri-)pancreatic pathology (MC expert) AND
- performance of at least 75 surgical procedures (nomenclature 242830–242841, 242852–242863, 242874–242885, 242896–242900).

The decision to define the minimal surgical volume of 75 procedures over three years was based upon statistical estimates. A minimal individual volume of 75 procedures was estimated to allow a statistical comparison of the postoperative mortality rates of the expert centres.

Patients discussed on MC in expert centre [1/7/2019 – 30/6/2022]

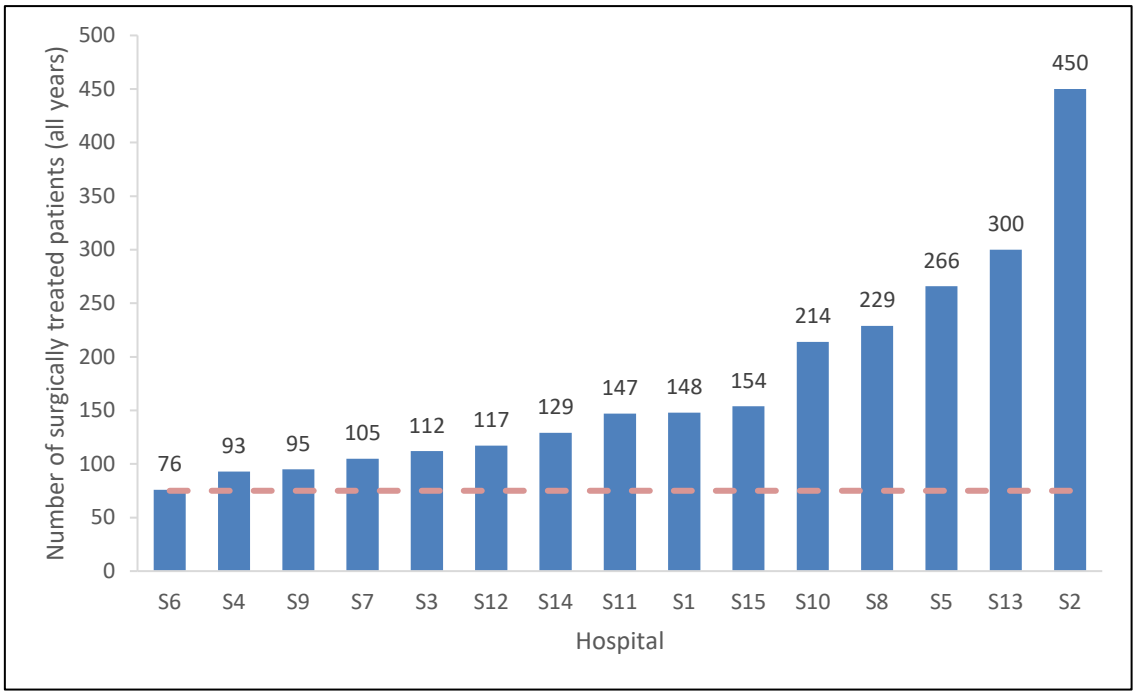


Funnel plot of the proportion of patients discussed on a MC that were treated surgically, by individual expert centre

In total, 6.569 patients were discussed on MC expert during the 3 convention years. On individual hospital level all 15 hospitals reached the minimum of 120 MC discussions over 3 years.

On average 40.1% of the discussed patients were subsequently selected for complex surgery. This proportion varied among the 15 centres between a minimum proportion of 27.6% and a maximum proportion of 56.5%.

Total surgical volume per expert centre [1/7/2019 – 30/6/2022]

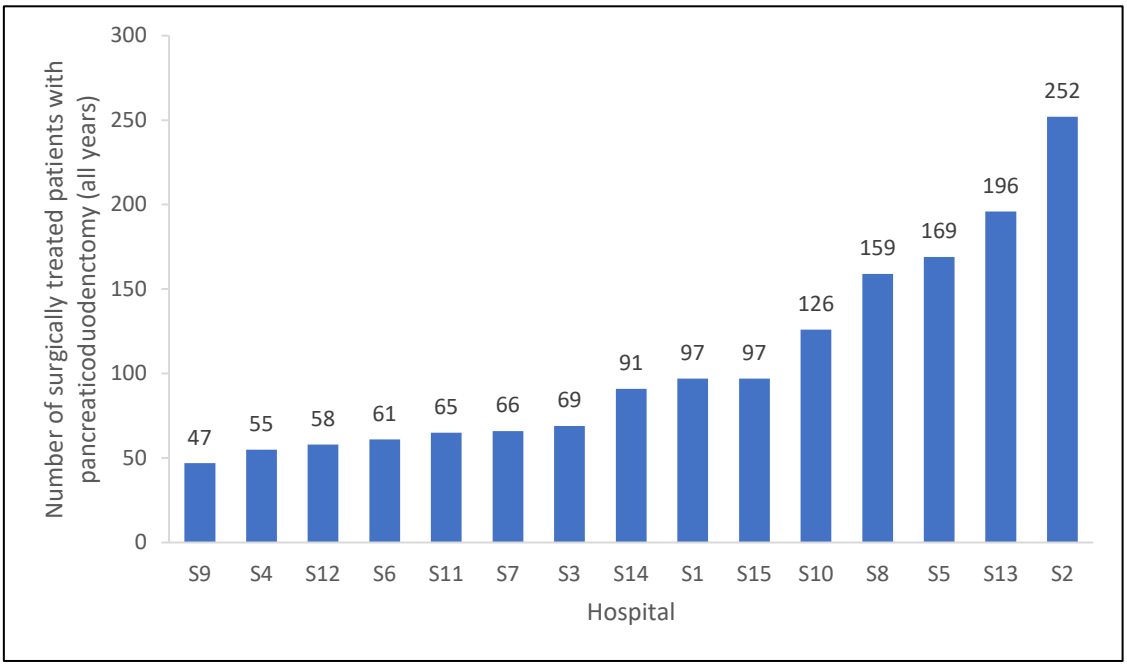


Absolute number of patients discussed on a MC expert that were treated surgically, by surgical centre

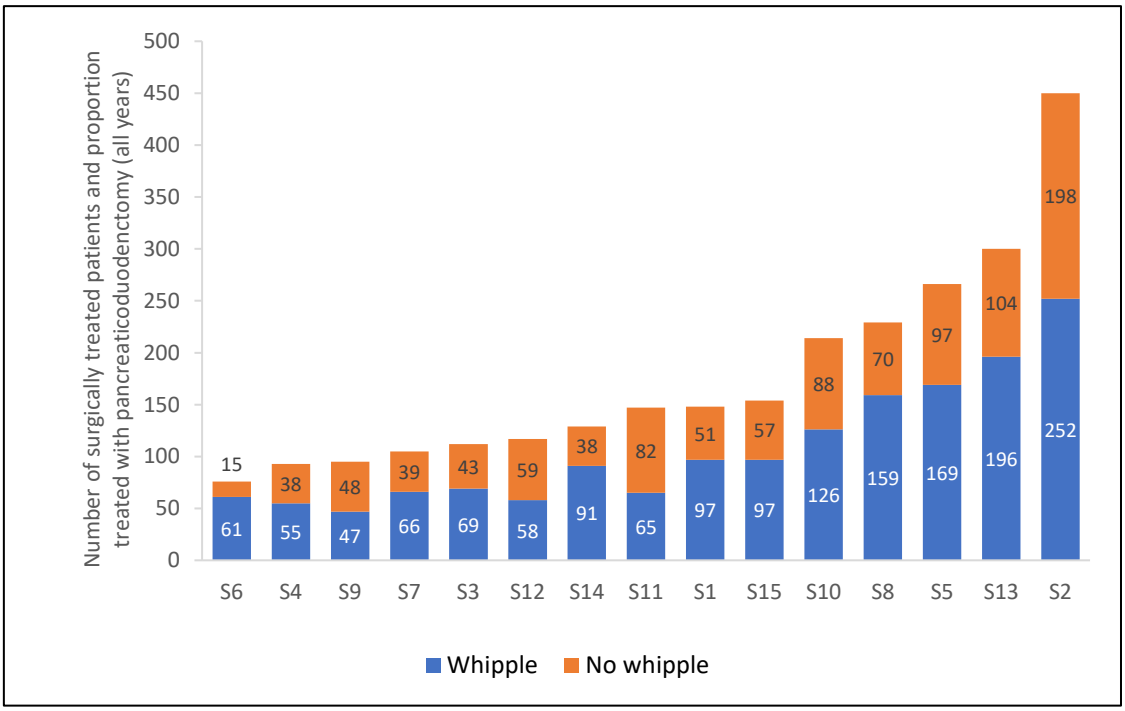
In total 2.635 complex surgical procedures (tumoural and non-tumoural pathology) were performed within the 3 convention years, 787 in year 1, 928 in year 2 and 920 in year 3. All of the 15 expert centres reached the minimum surgical volume of 75 after 3 years. The minimum individual surgical volume after 3 years was 76 and the maximum volume was 450.

The performed surgeries were carried out for malignant pathology in 78% (N=2.058).

Whipple volume per expert centre [1/7/2019 – 30/6/2022]



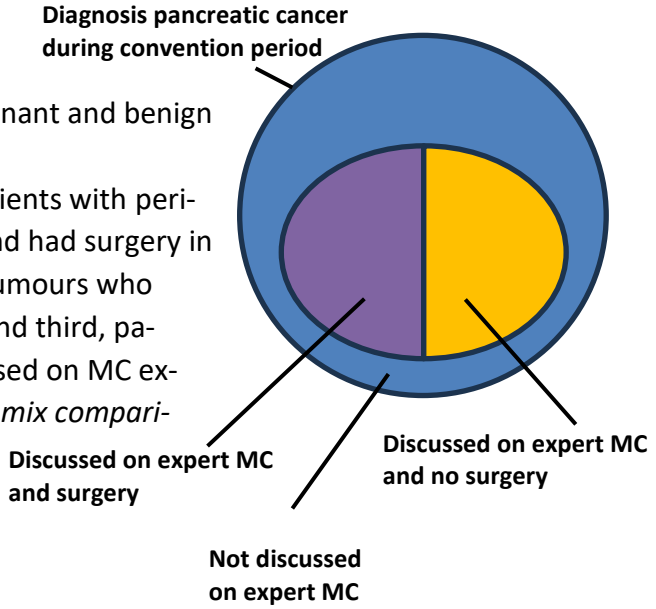
Absolute number of patients discussed on a MC expert that were treated with pancreaticoduodenectomy (Whipple), by surgical centre



Absolute number of patients discussed on a MC expert that were treated surgically (Whipple/no Whipple), by surgical centre

In total 1.608 Whipple (pancreaticoduodenectomy) procedures (tumoural and non-tumoural pathology) were performed within the 3 convention years, 512 in year 1, 548 in year 2 and 548 in year 3. The minimum individual Whipple volume after 3 years was 47 and the maximum volume was 252.

Delivered care for malignant and benign peri-pancreatic tumours



Description case-mix

To describe the patient and tumour characteristics, malignant and benign tumours will be described separately.
Also, 3 specific patient groups will be discussed. First, patients with peri-pancreatic tumours who were discussed on MC expert and had surgery in an expert centre, second, patients with peri-pancreatic tumours who were discussed on MC expert but did not have surgery, and third, patients with peri-pancreatic tumours who were not discussed on MC expert (only for malignant tumours). *See Appendix E – case mix comparisons*

MALIGNANT TUMOURS

1. Patients discussed on MC expert and selected for surgery

a) Description average case-mix of operated patients for the convention period (all patients) Appendix E, Table E1

During convention period, 2.085 patients with malignant peri-pancreatic tumours were selected for surgery, 1.115 (54%) males and 943 (46%) females (M/F ratio 1.2). The median age at the time of surgery was 68 years (IQR 57-73 years); the majority of the patients were 69 years or younger (56%) and 9% were older than 80 years. 56% of the patients were referred to an expert centre, the remaining 44% immediately presented at the expert centre.

The patients were classified by 3 different scoring systems to describe their comorbidities, the Charlson Comorbidity Index (CCI), the America Society of Anesthesiologists (ASA) score, and the WHO performance status. The majority of the patients were in good condition at the time of surgery (WHO score 0 or 1 in 88%). 41% of the patients had no comorbidity (CCI 0). Patients that were registered with comorbidities most commonly had concomitant diabetes without any damage to end-organs, chronic pulmonary disease, and peripheral vascular disease. 53% of the patients who had surgery had an ASA score of 2 (Mild systemic disease, normal activity).

The vast majority of the patients (97%) were operated for a primary pancreatic malignancy (N=1.990), 2% for a pancreatic tumour recurrence, and 1% for a metastasis. The primary pancreatic malignancies that were selected for surgery (N=1.990) were clinically stage 0, I, II, III and IV in 2%, 47%, 28%, 10% and 3%, respectively (for 10% the clinical stage was unknown). The main histological subtypes of the tumours were adenocarcinoma (AC) (77%) and neuroendocrine neoplasm (NEN) (15%). Most common tumour localisations were the

pancreatic head (45%) followed by the pancreatic tail (14%), the (peri-)ampullary region (10%) and the pancreatic body (9%).

Surgeries were most commonly carried out without any neoadjuvant treatment (83%), in 15% induction chemotherapy was delivered.

Of the 2.085 surgeries, 66% (N=1358) were pancreaticoduodenectomies, 5% total pancreatectomies, 28% hemi-pancreatectomies and 1% enucleations.

The initial surgical technique was open surgery in 62% versus minimal invasive surgery (MIS) in 38%; of the MIS techniques laparoscopy was the most frequently used. The proportion of patients treated with MIS for pancreatic cancer increased during the convention from 24% in year 1 to 39% in year 3. 15% (N=299) of the surgeries included a simultaneous venous resection and 2% (N=44) a simultaneous arterial resection.

b) Comparison of centre specific case-mix with average case-mix (all patients)

When comparing the expert centres regarding their case-mix, the median age of the patients at surgery ranged from 64 to 72 years. M/F ratio was higher than the average of 1.2 in 3 centres (1.5, 1.7 and 2.1 respectively). The distribution between AC and NEN was comparable among all centres. As mentioned, the patients were classified by 3 different scoring systems to describe their comorbidities, the CCI, the ASA score, and the WHO performance status. Differences in the distribution of these classifications between the centres were observed, but interpretation of the results is hampered by lack of consistency between the 3 different scoring systems within each centre.

In all centres, the distribution of the indications for surgical treatment (primary tumour/tumour recurrence/metastasis) was similar to the average distribution. The clinical stage distribution of the selected patients differed between the individual centres, but the multiple included tumour localizations (peri-pancreatic) and histological subtypes (AC and NEN) and the related differences in TNM classification makes the interpretation very difficult.

On average neoadjuvant chemotherapy was noted in 15% of the patients, in 2 centres the proportion was only 6%, contrasting with 2 centres where the proportions were 33% and 38%.

The proportion of Whipple surgeries (pancreaticoduodenectomies) varied between the centres from 52% to 83% of all procedures, the proportion of enucleations was similar among all centres.

Finally, on average the initial surgical technique was open surgery in 62% versus MIS in 38%, however important variation exists between the individual centres. In 3 centres open surgery was carried out in more than 90%, contrasting with 1 centre where only 3% of the

surgeries were open surgery. Also, variation between the centres exists as for the type of MIS technique (laparoscopic versus robotic or hybrid).

c) Comparison of average case-mix operated patients convention with average T0(2015-2018) results (only primary tumours) Appendix E, Table E2

When comparing the average convention case-mix with the average $T0_{2015\text{-}2018}$ case-mix, only the primary tumours are selected in the convention, N=1.990, and compared with $T0_{2015\text{-}2018}$ N_{T0}=2.262.

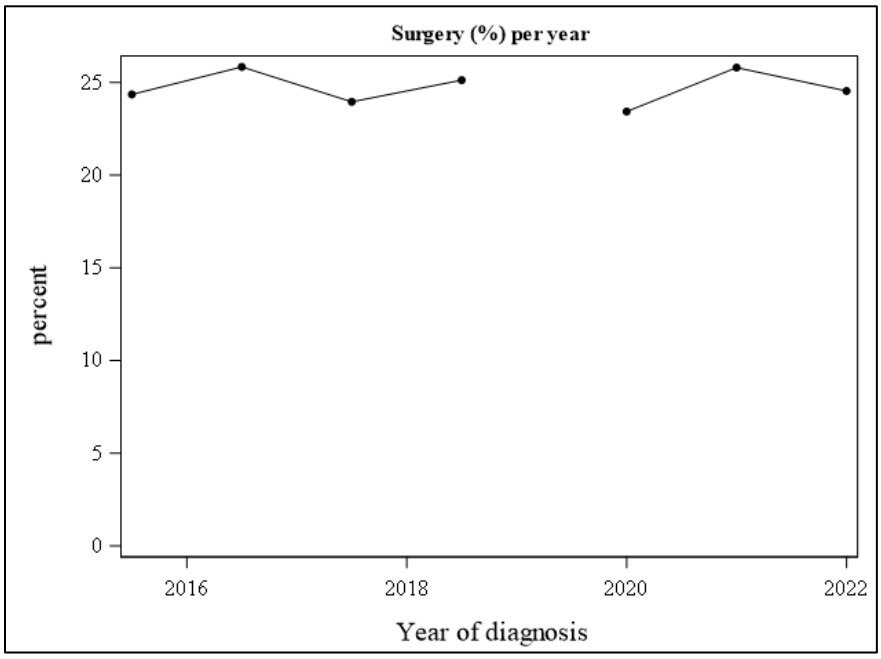
The median age of the patients at surgery, M/F ratio and distribution between AC and NEN was comparable.

Evaluation of the clinical stage of the patients that were selected for surgery in the 2 periods was hampered by the large proportion of unknown clinical stages (44%) in $T0_{2015\text{-}2018}$ compared to the convention (10%), together with the already mentioned heterogeneity regarding TNM classification of the various peri-pancreatic tumours. Nevertheless, in both periods the largest share of the patients with known clinical stage had tumours stage I or II. No remarkable differences are observed as for clinical stage between the 2 periods.

The proportion of the patients that received neoadjuvant treatment increased slightly in the convention period (N=344; 15%) compared to $T0_{2015\text{-}2018}$ (N=220; 10%).

d) Observed trends in time

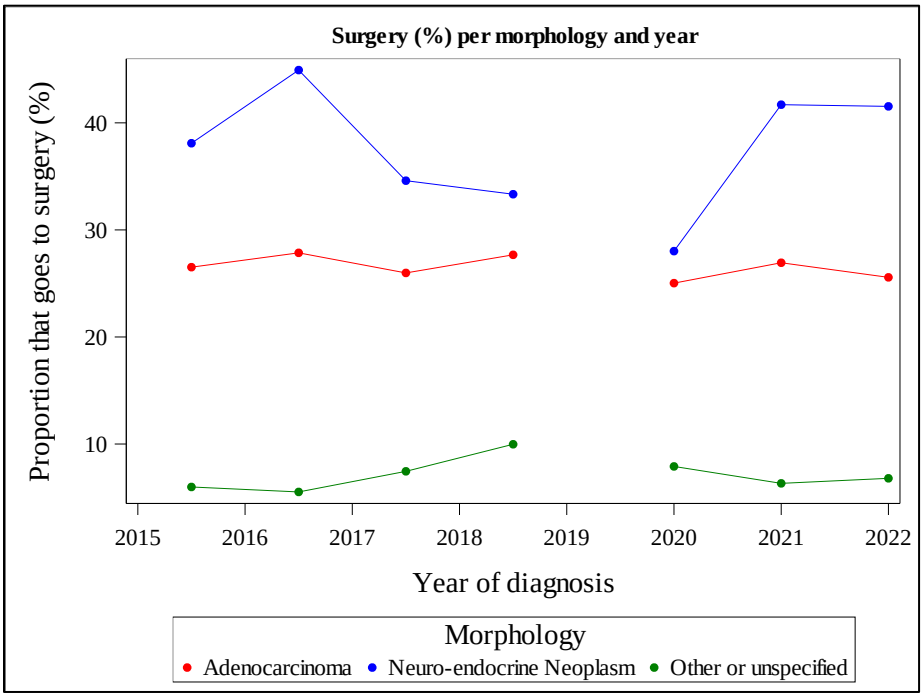
- *Proportion of peri-pancreatic malignant tumours that is selected for surgery*



Percentage of the total incidence of peri-pancreatic malignant tumours that received surgery

The proportion of primary malignant tumours of the peri-pancreas that is selected for surgical treatment appears to be more or less stable in time and varies around 25%.

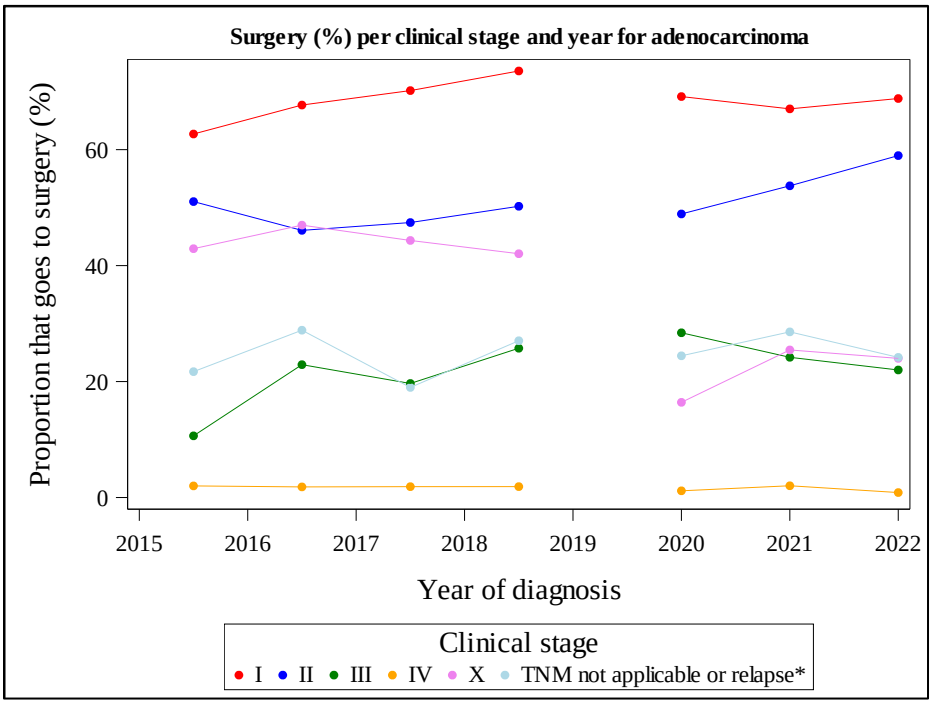
- *Proportion of peri-pancreatic malignancies that is selected for surgery by histological sub-type*



Percentage of the total incidence of peri-pancreatic malignant tumours that received surgery, by histological subtype

The proportion of primary AC of the peri-pancreas that is selected for surgical treatment appears to be more or less stable in time and varies around 25%, the proportion of NEN that goes to surgery varies more in time and in general lies a bit higher around 40%.

- *Proportion of adenocarcinoma of the peri-pancreas that is selected for surgery, by clinical stage*



Percentage of the total incidence of peri-pancreatic adenocarcinoma that received surgery, by clinical stage

No impressive trends are observed as for the tumours that are selected for surgery by clinical stage. A slight increase of the proportion of clinical stage II tumours that are selected for surgery is observed, besides more or less stable proportions for clinical stage I, III and IV.

2. Patients discussed on MC expert but not selected for surgery

a) Description average case-mix of patients discussed on MC but not selected for surgery for the convention period (all patients)

During the convention period, 2.306 patients were discussed on MC expert for a malignant peri-pancreatic tumour for whom it was decided not to perform surgery. Of these patients there were 1.206 (52%) males and 1100 (48%) females. The median age at the time of surgery was 71 years (IQR 63-78 years). The majority of the patients were in good condition at the time of MC (WHO score 0 or 1 in 62%), 9% was scored with WHO 2, and for 26% there was no information registered on WHO score. 96% of the patients were discussed because of a primary malignancy (N=2.221), 2% because of a tumour recurrence, and 2% because of a metastasis. The main histological subtypes of the tumours were AC (79%) and NEN (7%), 14% of the tumours had a different or unspecified histological subtype.

b) *Comparison of characteristics of patients discussed on MC expert that were selected for surgery versus patients that were not selected for surgery (all patients) Appendix E, Table E3*

When comparing the average convention case-mix of patients with a malignant peri-pancreatic tumour selected for surgery (N=2.058; surgery group) with the average convention case-mix of patients with a malignant peri-pancreatic tumour not selected for surgery (N=2.306; no surgery group), there were no differences as for the type of lesion to treat: 96-7% primary tumours, 2% tumour recurrences, very few metastases. The age distribution of the patients was different, with a younger median age in the surgery group (68) versus the no surgery group (71), in the surgery group 9% was 80 or older versus 22% in the no surgery group. M/F ratios were similar. The distribution between AC and NEN is difficult to evaluate because in the no surgery group the proportion with 'other or unspecified histology' is larger (14%) than in the surgery group (8%). As mentioned, there is an important heterogeneity regarding TNM classification of the various peri-pancreatic tumours that hampers comparison between the 2 groups, nevertheless the proportion of clinical stage IV tumours is, as expected, remarkably larger in the no surgery group (48% versus 3% in the surgery group). Finally, the patients that were selected for surgery were referred to the expert centre in 56%, whereas the patients for which it was decided not to offer surgery were referred to the expert centre in 45%.

3. Patients not discussed on MC expert (period 1/7/2019 – 31/12/2021)

The convention didn't impose a discussion of every patient diagnosed with a new peri-pancreatic cancer on an MC in an expert centre. Therefore, a part of the peri-pancreatic cancer incidence is not captured within the convention. The following results describe this specific population.

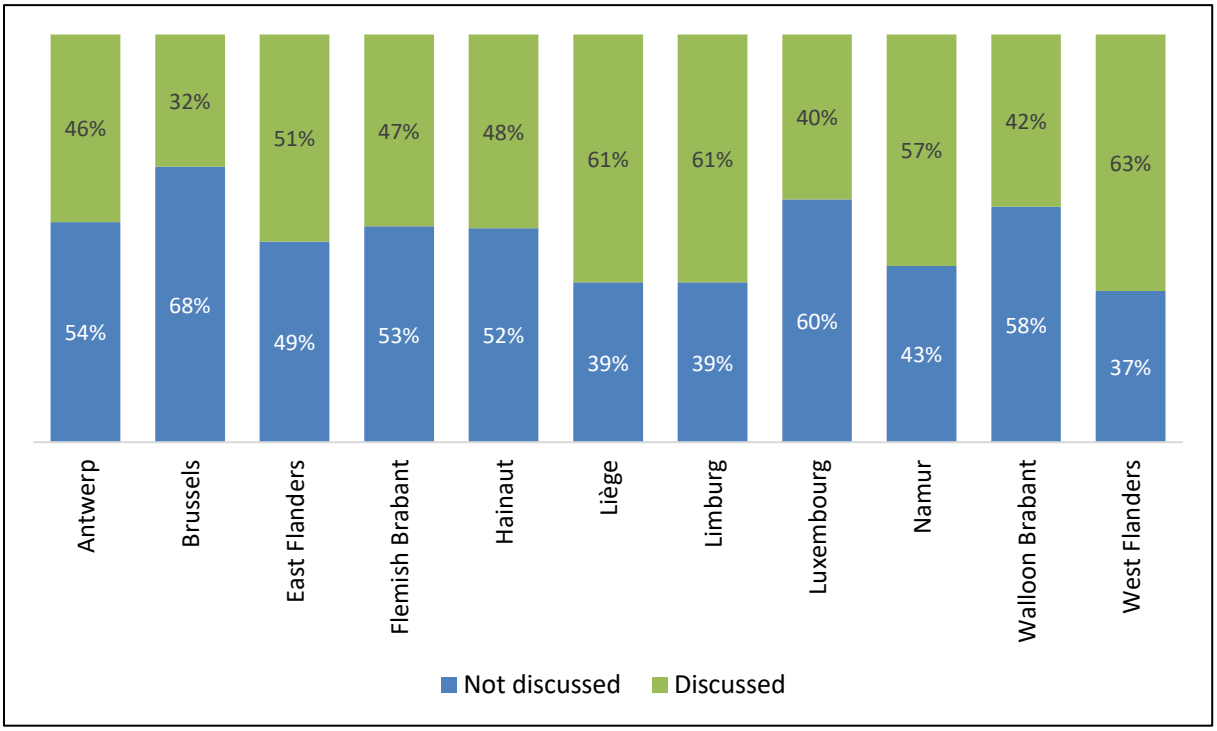
a) Description average case-mix of patients that were not discussed on MC expert for the convention period 1/7/2019 – 31/12/2021 (only primary tumours)

During the convention period 1/7/2019 – 31/12/2021, 3.227 patients diagnosed with peri-pancreatic cancer and notified through the classical cancer registration were not discussed on a MC expert. Of these patients there were 1.658 (51%) males and 1.569 (49%) females. The median age at diagnosis was 74 years (IQR 65-82), 35% of the patients were 69 or younger, 31% between 70 and 79 and 34% was 80 or older. Histologically, 69% of the tumours were AC and 9% NEN. The tumours were clinically stage 0, I, II, III and IV in 0%, 11%, 8%, 7% and 63% (for 12% the clinical stage was unknown).

b) *Comparison of case-mix characteristics of patients **discussed on MC expert** (period 1/7/2019 – 30/6/2022) versus patients **not discussed on MC expert** (period 1/7/2019 – 31/12/2021) (only primary tumours) Appendix E, Table E5*

During the convention period 1/7/2019 – 30/6/2022, 4.208 patients diagnosed with primary peri-pancreatic cancer were discussed on MC expert, whereas 3.227 newly diagnosed patients in the period 1/7/2019 – 31/12/2021 were not discussed on expert MC (=population not discussed). The patients that were discussed on MC expert were statistically significantly younger than those who were not discussed on MC expert (median age 70 years versus 74 years; p<0.0001), 17% of the convention population was 80 years or older compared to 34% of the population not discussed. M/F ratio was 1.1 in both the convention population and the population not discussed. Remarkable differences were observed as for the clinical stage of the patients, in the convention population, a larger proportion is seen of stage 0, I, II and III tumours (66% compared to 26% in the population not discussed) and conversely the proportion of stage IV and unknown stage tumours is smaller (27% stage IV and 7% stage unknown compared to 63% and 12% in the population not discussed).

Furthermore, there are differences between the 11 provinces in Belgium in terms of the proportion of the patients with newly diagnosed peri-pancreatic cancer residing in a particular province that are (not) discussed on an expert MC.



Percentage of the total incidence of peri-pancreatic malignancies in a specific province that was discussed or not discussed on a specialized expert MC

The figure demonstrates for each province the total number of patients with newly diagnosed peri-pancreatic cancer (100%), and shows the proportion of patients that was discussed or was not discussed on an expert MC. A higher % of patiënts residing in Brussels (68%), Luxembourg (60%) and Walloon Brabant (58%) were not discussed on an expert MC, whereas in West Flanders (37%), Liège (39%), Limburg (39%) and Namur (43%) the proportion of not discussed patients was lower.

BENIGN TUMOURS

1. Patients discussed on MC expert and selected for surgery

a) Description average case-mix of operated patients for the convention period (all patients) Appendix E, Table E1

During the convention period, 373 patients with benign peri-pancreatic tumours were selected for surgery, 185 (50%) males and 188 (50%) females (M/F ratio 1.0). The median age at the time of surgery was 65 years (IQR 57-73 years). The patients were also classified by 3 different scoring systems to describe their comorbidities, the CCI, the ASA score, and the WHO performance status. The majority of the patients were in good condition at the time of surgery (WHO score 0 or 1 in 94%). 45% of the patients had no comorbidity (CCI 0). Patients that were registered with comorbidities most commonly had concomitant diabetes without any damage to end-organs, chronic pulmonary disease, and peripheral vascular disease. 58% of the patients who had surgery had an ASA score of 2 (Mild systemic disease, normal activity).

The most common histological subtypes of the tumours were Intraductal Papillary Mucinous Neoplasms (IPMN) (55%) and cystadenoma (24%). Of the 373 surgeries, 39% (N=146) were pancreaticoduodenectomies, 8% total pancreatectomies, 49% hemi-pancreatectomies and 4% enucleations. The initial surgical technique was open surgery in 38% versus MIS in 62%.

b) Comparison of centre specific case-mix with average case-mix (all patients)

The comparison of the different expert centres regarding their case-mix is currently not informative because the individual volumes are too low.

2. Patients discussed on MC expert but not selected for surgery

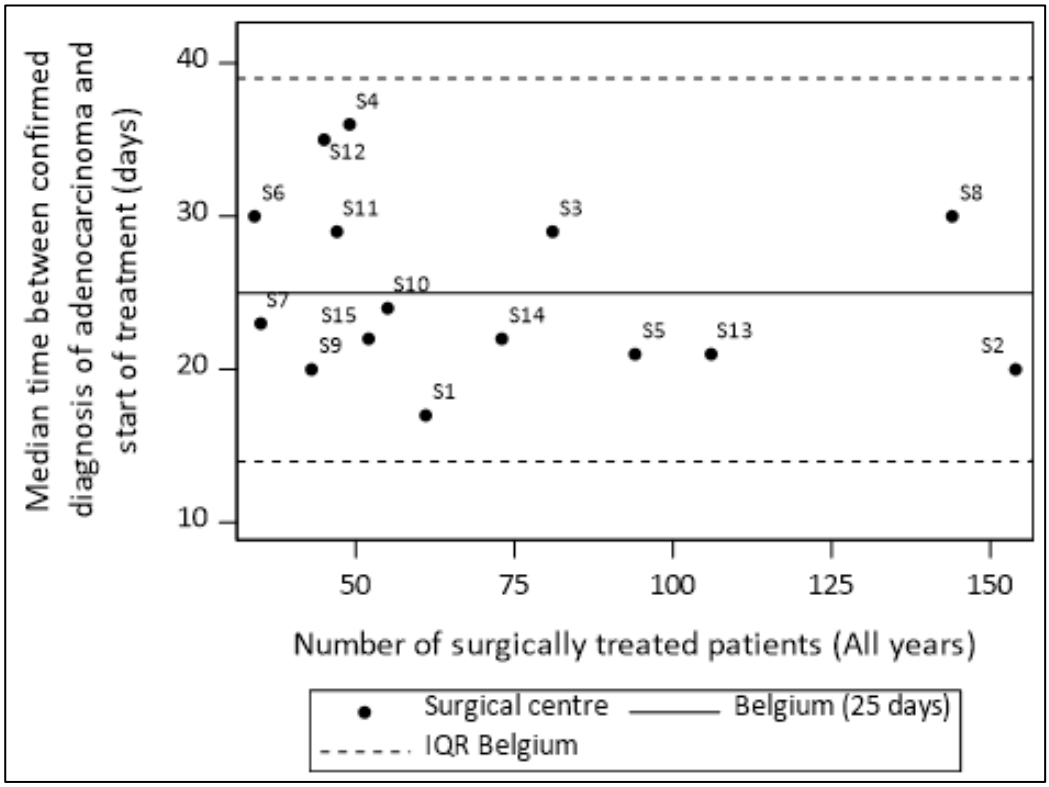
During convention period, 1.029 patients with benign peri-pancreatic tumours were discussed on MC expert but not selected for surgery, 407 (40%) males and 622 (60%) females (M/F ratio 0.7). The median age at the time of MC discussion was 70 years (IQR 61-76 years). The most common histological subtypes of the tumours that were discussed but not selected for surgery IPMN (70%) and cystadenoma (15%). *Appendix E, Table E4*

3. Patients not discussed on MC expert

As benign tumoural pathology is not notified through the cancer registration, there are no data available for the patients with benign tumoural pathology of the peri-pancreas that were not discussed on MC in an expert centre.

Median time between anatomopathologically confirmed diagnosis and start of any treatment (for adenocarcinoma only)

a) Description average results for the convention and centre specific results *(Appendix F)*



Patients with peri-pancreatic AC that received surgery had a median time between confirmed diagnosis and start of *any first* treatment of 25 days (IQR 14-39). The median time to first treatment was similar for patients who presented immediately at the expert centre and those who were referred to an expert centre, namely 24 days (IQR 13-39) versus 25 days (IQR 14-39) (p=0.3669).

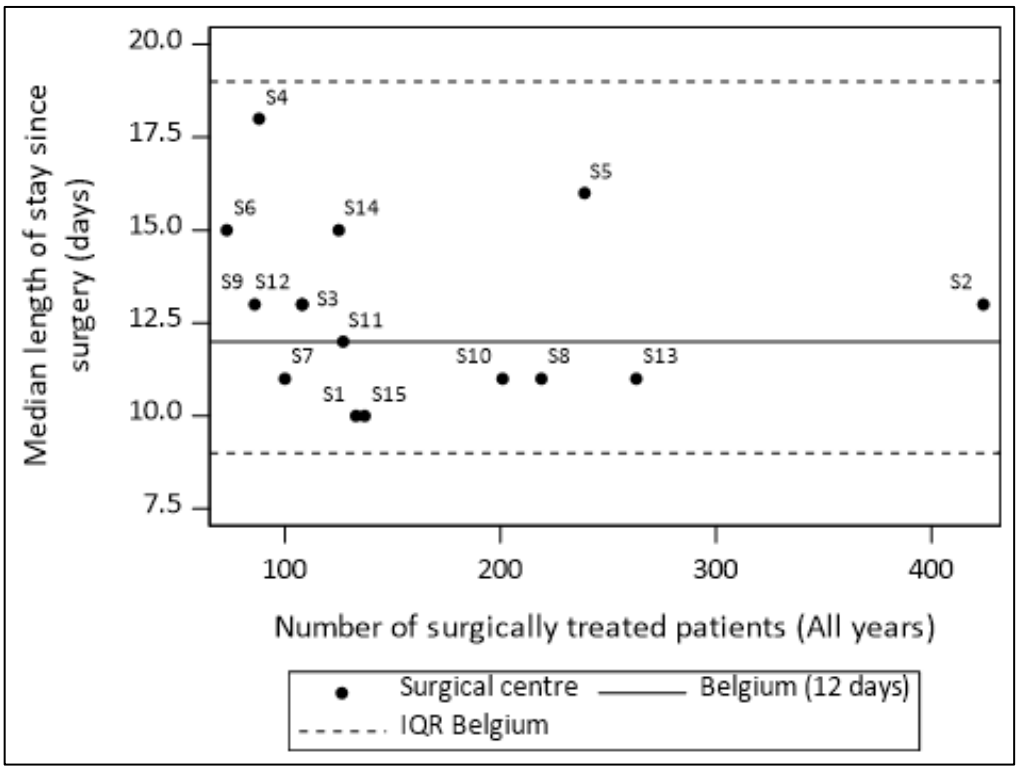
On individual expert centre level, median time to first treatment of AC was comparable or shorter than the overall median for 9/15 centres, 6 centres had a longer median time to first treatment to the maximum median time of 36 days (IQR 26-50).

b) Comparison of average convention results for *all operated primary adenocarcinoma* with average $T0_{(2015\text{-}2018)}$ results

The median time between confirmed diagnosis and start of any first treatment (options regarded as first treatment being chemotherapy, radiotherapy or surgery) for the patients in $T0_{2015\text{-}2018}$ (N=1.826) was 17 days (IQR 0-30), compared to the convention result of 19 days (IQR 0-33) for primary adenocarcinoma with surgery during the convention (N=1.553).

Length of stay in the expert centre (malignant + benign tumours)

a) Description average results for the convention and centre specific results *(Appendix F)*



Patients with benign or malignant tumours of the peri-pancreas that underwent surgery had a median length of hospital stay of 12 days (IQR 9-19). In 7 expert centres the median length of stay was longer than the overall result, the longest median length of hospital stay was 18 days (IQR 12-29).

For all expert centres together, the median length of stay for pancreaticoduodenectomies and/or total pancreatectomies was 14 days (IQR 10-21), compared with a median hospital stay of 10 days or shorter for the subtotal pancreatic surgeries.

b) Comparison of average convention results with average $T0_{(2015\text{-}2018)}$ results

Data on length of hospital stay are not available for the T0 period.

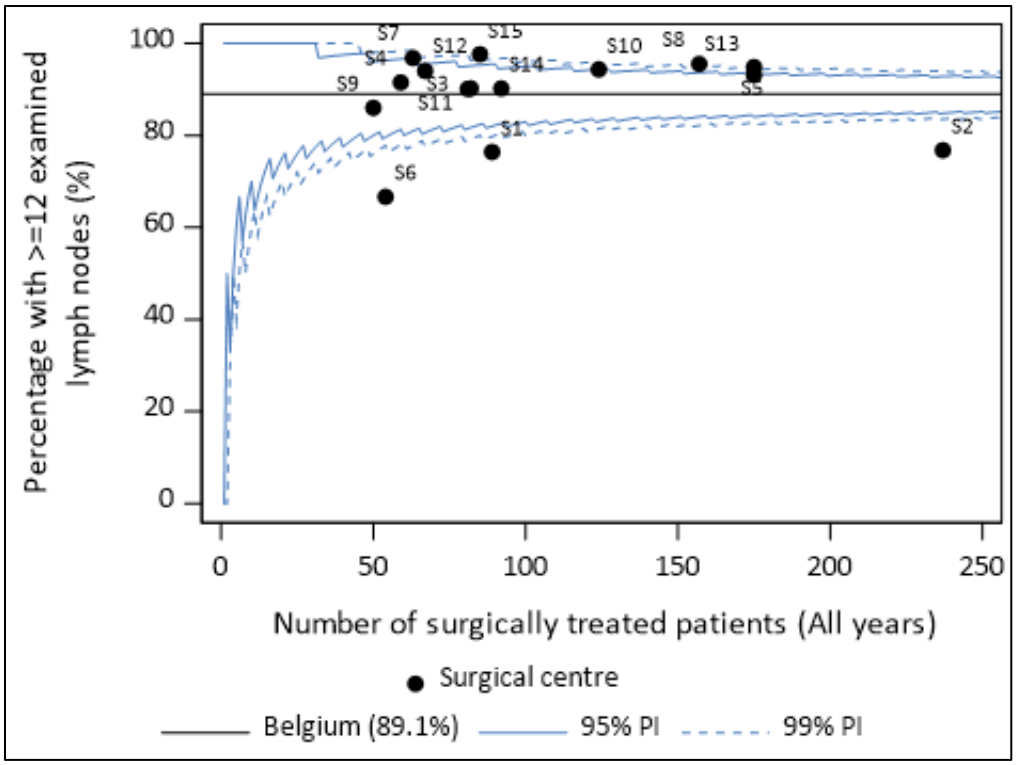
Proportion of surgically treated patients with >= 12 LN examined (only for adenocarcinoma)

The number of examined lymph nodes is an acknowledged parameter related to the survival after pancreatectomy for pancreatic cancer, and although the optimal number of nodes remains subject of debate, according to the AJCC Cancer Staging Manual 8th edition, a minimum of 12 nodes must be recovered for lymph node staging to be considered accurate in

curative resections.[3-5] An important drawback remains the lack of standardization as for lymphadenectomy on the one hand and the pathological work-up on the other hand. Concerns were raised by the clinical experts as for the reporting of the number of resected lymph nodes. It was said that there was no clear standard as for which lymph nodes needed to be counted, and that therefore important variation in the way of reporting exists between the different expert centres.

a) Description average results for the convention and centre specific results, *adenocarcinoma only* *(Appendix F)*

On average, in 89% of the patients with AC ≥12 lymph nodes were examined. The average result increased from 88% in the first two years to 91% in the third year of the convention.



In 4 expert centres, ≥12 lymph nodes were examined in less than the average result of 89% of the patients (with the minimal centre result being 67%).
In all expert centres together, for pancreaticoduodenectomy and/or total pancreatectomy procedures the average result was 92%, compared to 80% or less for subtotal pancreatectomies.

b) Comparison of average convention results with average $T0_{(2015\text{-}2018)}$ results

Data on number of examined lymph nodes are not available for the T0 period.

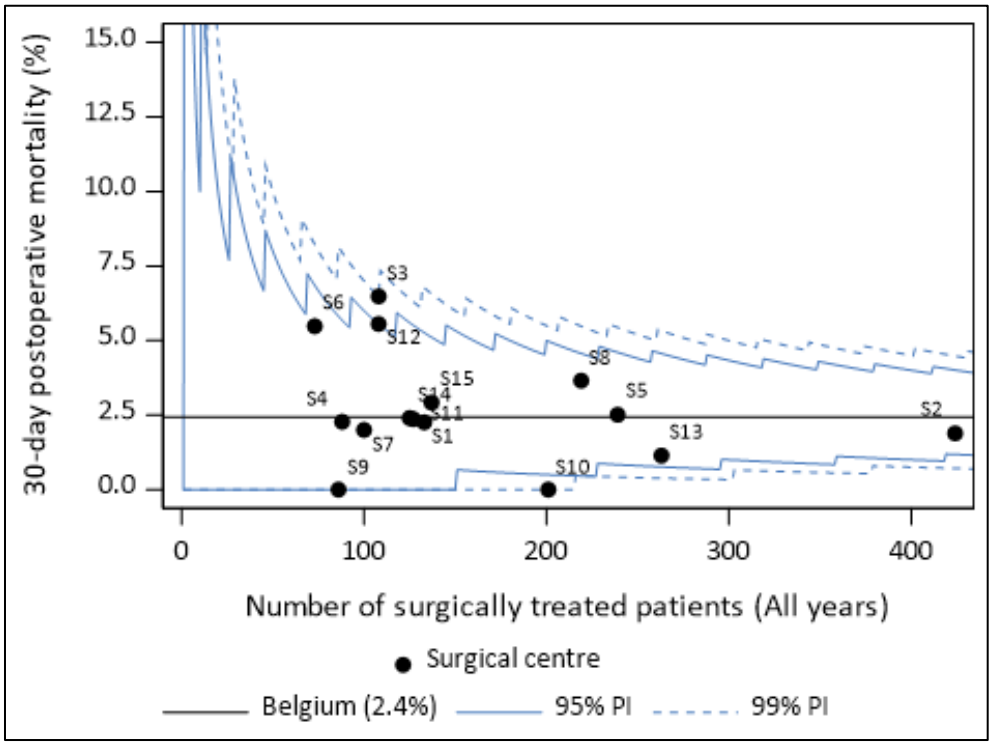
Mortality

1. 30-day postoperative mortality

Remark: COVID-19 crisis
Remarks were made by clinicians to exclude mortality cases related to COVID-19 from the results. It was decided that based on international scientific standards, reported mortality should include all possible causes of death.

a. Description average results for the convention and centre specific results

Unadjusted 30-day postoperative mortality, malignant + benign tumours (Appendix F)
The overall observed 30-day postoperative mortality after pancreatic surgery over 3 years is 2.4% (95%CI [1.9, 3.1]) (59 deaths over 2.431). During the 3 years, 30-day postoperative mortality remained fairly stable, namely 2.5% in the first year, 2.2% in the second year, and 2.6% in the third year. For information, in 4 cases (4/59) COVID-19 was mentioned in the description of the cause of death for the 30-day mortality.



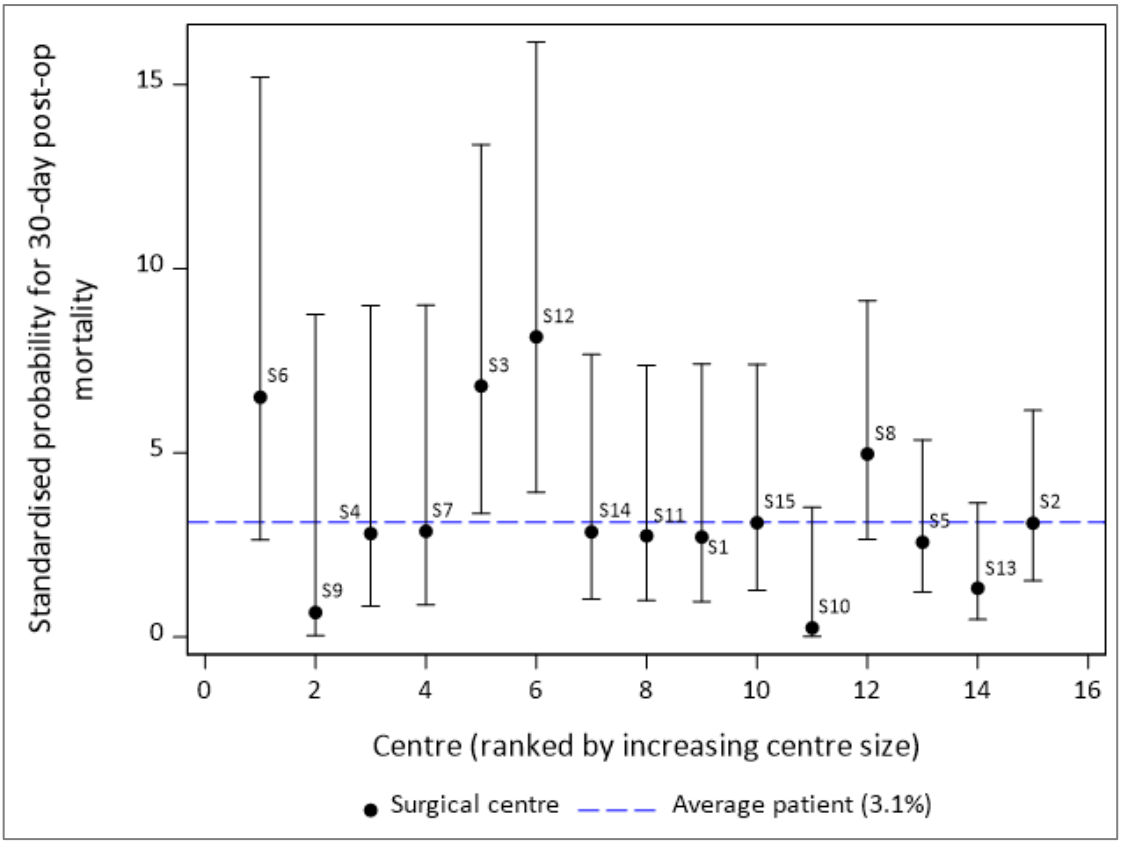
The average centre specific results for 30-day postoperative mortality ranged between 0% 95%CI [0.0, 4.2] up to 6.5% 95%CI [2.6, 12.9], 5 centres had a higher observed 30-day postoperative mortality than the Belgian average.

Adjusted 30-day postoperative mortality, malignant + benign tumours

To enable comparison of the centre-specific results, case-mix adjusted odds ratios (OR) for postoperative mortality within 30 days and the centre specific direct standardized 30-day mortality rates (%), together with their accompanying 95% confidence intervals, are calculated. The adjustment factors were selected by the Belgian Pancreatic Cancer Group (BPCG). The 'average patient' OR and direct standardized result are weighted averages of the individual centre results with the fraction of patients per centre as weights. The 'average patient' results for the case-mix adjusted OR and the direct standardized mortality serve as references and enable comparison of the individual centre results with the reference. An individual centre result is significantly different from the average result if the average result is not included in the centre specific confidence interval.

	Adjusted Odds Ratio			Standardised probability (%)		
Expert centres	Estimate	95% CI	Average patient	Estimate	95% CI	Average patient
S1	1.03	[0.36, 2.99]	1.22	2.7	[1.0, 7.4]	3.1
S2	1.18	[0.53, 2.64]	1.22	3.1	[1.5, 6.2]	3.1
S3	2.78	[1.26, 6.14]	1.22	6.8	[3.4, 13.4]	3.1
S4	1.07	[0.32, 3.60]	1.22	2.8	[0.8, 9.0]	3.1
S5	0.98	[0.44, 2.17]	1.22	2.6	[1.2, 5.4]	3.1
S6	2.64	[1.00, 6.97]	1.22	6.5	[2.6, 15.2]	3.1
S7	1.09	[0.33, 3.61]	1.22	2.9	[0.9, 9.0]	3.1
S8	1.96	[0.96, 4.01]	1.22	5.0	[2.6, 9.1]	3.1
S9	0.24	[0.02, 3.01]	1.22	0.7	[0.0, 8.8]	3.1
S10	0.09	[0.01, 1.13]	1.22	0.3	[0.0, 3.5]	3.1
S11	1.04	[0.37, 2.96]	1.22	2.7	[1.0, 7.4]	3.1
S12	3.40	[1.48, 7.82]	1.22	8.2	[3.9, 16.2]	3.1
S13	0.49	[0.18, 1.37]	1.22	1.3	[0.5, 3.6]	3.1
S14	1.09	[0.38, 3.08]	1.22	2.9	[1.0, 7.7]	3.1
S15	1.19	[0.46, 3.04]	1.22	3.1	[1.3, 7.4]	3.1

Adjusted for age at diagnosis, sex, ASA score, Charlson Comorbidity Index, type of surgery, vascular resection/reconstruction and tumor type (as proposed by the Belgian Pancreatic Cancer Group).



The postoperative mortality probability was modelled using a logistic regression model. All the possible two-way interaction terms between the case-mix variables were evaluated during the model building procedure. The quality of the regression was assessed taking into account the deviance as well as Pearson goodness-of-fit and the Hosmer and Lemeshow goodness-of-fit test, and the residual plots were examined for potential influential points and resolved when needed.

The average direct standardized 30-day postoperative mortality after pancreatic surgery for malignant and/or benign tumours was 3.1%. 2 centres had a significantly higher postoperative mortality than the average, namely 6.8% 95%CI [3.4, 13.4] and 8.2% 95%CI [3.9,16.2], all other centres performed statistically not different from the average result.

b. Comparison of average convention results for *all operated primary malignant tumours* with average $T0_{(2015\text{-}2018)}$ results

The overall unadjusted 30-day postoperative mortality during the $T0_{2015\text{-}2018}$ period (N=2.261) was 4.3% 95%CI [3.5, 5.2]. During the convention period the unadjusted result including all operated *primary malignant* tumours (N=1.987) was 2.6% 95%CI [2.0, 3.4].

When adjusting both results for case-mix characteristics (age group, sex, WHO performance score, type of surgery (pancreaticoduodenectomy versus subtotal pancreas resection)), the adjusted OR for the convention period - with the $T0_{2015\text{-}2018}$ period as the reference - was 0.626 95%CI [0.43-0.91]. Therefore, the decreasing trend that is observed in the unadjusted overall 30-day postoperative mortality during the convention in comparison to the $T0_{2015\text{-}2018}$ period is proven to be statistically significant (p=0.016).

2. 90-day postoperative mortality

The Belgian results for 90-day mortality after peri-pancreatic surgery that were provided by the BCR for the period 2008-2018 revealed significant differences according to the annual hospital volume. Overall unadjusted 90-day postoperative mortality in Belgian hospitals was 7.8%, and it was shown that in the hospitals having an annual volume of at least 20 surgeries in this time period, 90-day postoperative mortality was significantly lower compared to the hospitals having an annual volume of less than 6 surgeries, with an adjusted OR of 0.49 95%CI [0.3, 0.7] p=0.0005.

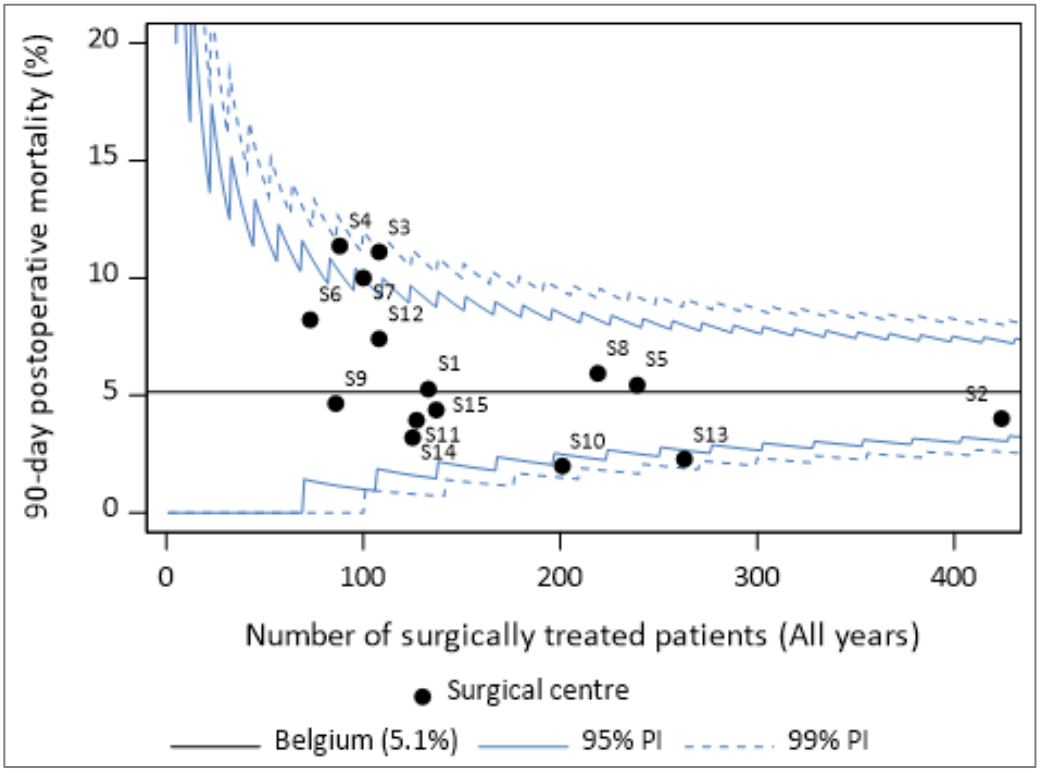
a. Description average results for the convention and centre specific results

Unadjusted 90-day postoperative mortality, malignant + benign tumours (Appendix F)

The overall observed 90-day postoperative mortality after pancreatic surgery over the 3 years is 5.1% (95%CI [4.3, 6.1]) (125 deaths over 2.431). During the 3 years, 90-day postoperative mortality remained fairly stable, namely 4.6% in the first year, 5.5% in the second year, and 5.6% in the third year.

Cause of death between 30 and 90 days after surgery

When reviewing all the reported causes of death that occurred between 30 and 90 days after surgery (N=66), 63/66 were specified. 13/63 deaths (21%) were related to progressive disease. For 8/63 (13%) deaths palliative care or euthanasia was mentioned. In 2/63 (3%) reported causes of death a relation with COVID-19 was mentioned.



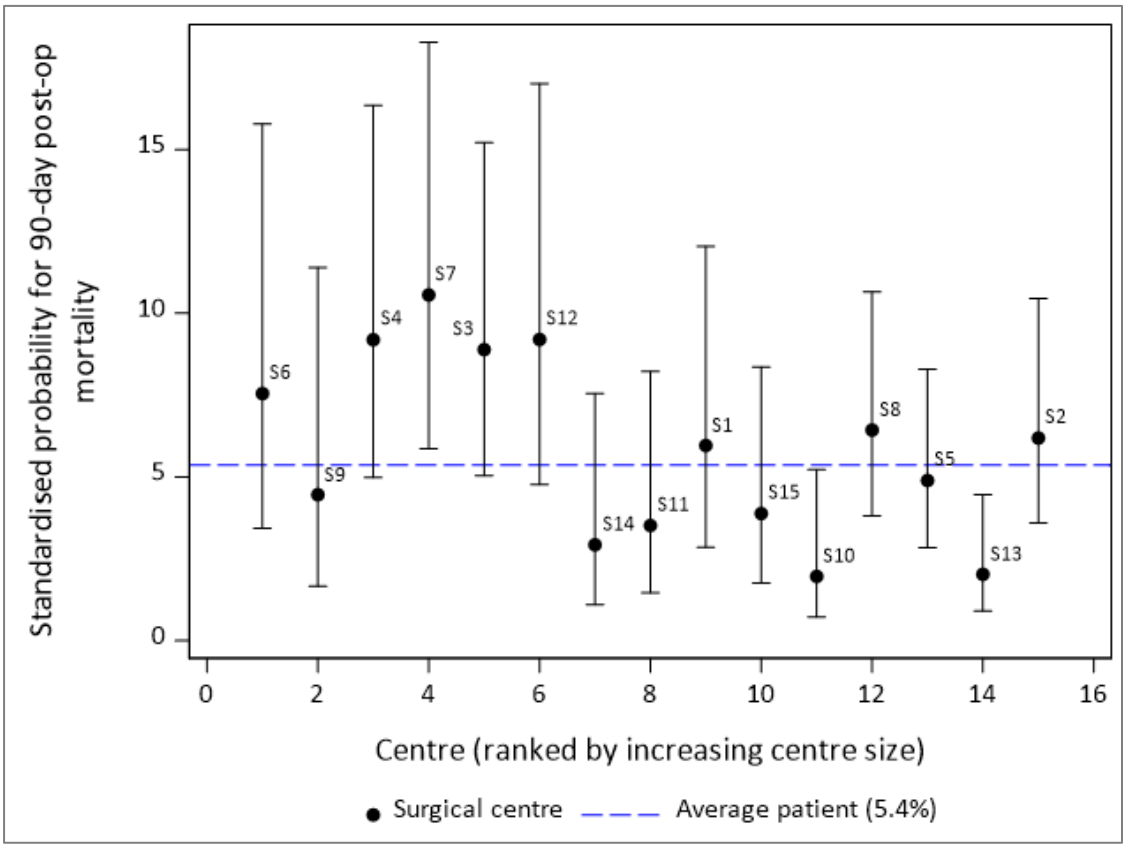
The average centre specific results for the unadjusted 90-day postoperative mortality ranged between 2.0% CI [0.5, 5.0] up to 11.4% CI [5.6, 19.9], 7 centres had a higher observed 90-day postoperative mortality than the Belgian average.

Adjusted 90-day postoperative mortality, malignant + benign tumours

The adjustment factors were selected by the Belgian Pancreatic Cancer Group (BPCG).

	Adjusted Odds Ratio			Standardised probability (%)		
Expert centres	**Esti-mate**	**95% CI**	**Average patient**	**Esti-mate**	**95% CI**	**Average patient**
S1	1.16	[0.53, 2.52]	1.05	6.0	[2.9, 12.0]	5.4
S2	1.21	[0.65, 2.24]	1.05	6.2	[3.6, 10.5]	5.4
S3	1.82	[0.97, 3.40]	1.05	8.9	[5.0, 15.2]	5.4
S4	1.89	[0.96, 3.71]	1.05	9.2	[5.0, 16.4]	5.4
S5	0.93	[0.52, 1.67]	1.05	4.9	[2.8, 8.3]	5.4
S6	1.51	[0.66, 3.46]	1.05	7.5	[3.4, 15.8]	5.4
S7	2.22	[1.15, 4.31]	1.05	10.6	[5.9, 18.3]	5.4
S8	1.26	[0.71, 2.23]	1.05	6.4	[3.8, 10.7]	5.4
S9	0.84	[0.31, 2.28]	1.05	4.5	[1.7, 11.4]	5.4
S10	0.36	[0.13, 0.94]	1.05	2.0	[0.7, 5.2]	5.4
S11	0.65	[0.27, 1.58]	1.05	3.5	[1.5, 8.2]	5.4
S12	1.89	[0.91, 3.90]	1.05	9.2	[4.8, 17.0]	5.4
S13	0.37	[0.17, 0.81]	1.05	2.0	[0.9, 4.5]	5.4
S14	0.54	[0.21, 1.42]	1.05	2.9	[1.1, 7.6]	5.4
S15	0.73	[0.32, 1.63]	1.05	3.9	[1.8, 8.4]	5.4

Adjusted for age at diagnosis, sex, ASA score, Charlson Comorbidity Index, type of surgery, vascular resection/reconstruction and tumor type (as proposed by the Belgian Pancreatic Cancer Group).



This table and figure show the case-mix adjusted odds ratio for postoperative mortality within 90 days and the centre specific direct standardized 90-day mortality (%), together with their accompanying 95% confidence intervals. Interpretation and modelling is similar to results for the 30 day postoperative mortality (cfr supra).

The average direct standardized 90-day postoperative mortality after pancreatic surgery for malignant and/or benign tumours was 5.4%. One centre had a significantly higher postoperative mortality than the average, namely 10.6% 95%CI [5.9, 18.3], 2 centres had a significantly lower mortality, namely 2.0% 95%CI [0.7, 5.2] and 2.0% 95%CI [0.9, 4.5], all other centres performed statistically not different from the average result.

b. Comparison of average convention results for *all operated primary malignant tumours* with average $T0_{(2015\text{-}2018)}$ results

The overall unadjusted 90-day postoperative mortality during the $T0_{2015\text{-}2018}$ period (N=2.261) was 7.3% 95%CI [6.3, 8.4]. During the convention period the unadjusted result including all operated *primary malignant* tumours (N=1.987) was 5.6% 95%CI [4.7, 6.7].

When adjusting both results for case-mix characteristics (age group, sex, WHO performance score, type of surgery (pancreaticoduodenectomy versus subtotal pancreas resection)), the adjusted OR for the convention period - with the $T0_{2015\text{-}2018}$ period as the reference - was 0.788 95%CI [0.60-1.03]. Therefore, although there is a decreasing trend that is observed in the unadjusted overall 90-day postoperative mortality during the convention in comparison to the $T0_{2015\text{-}2018}$ period, the difference was not statistically significant (p=0.083).

Survival

In Belgium, overall 5yRS of peri-pancreatic cancer is 16.9% (period 2016-2021).

Survival rates vary substantially according to the stage at diagnosis, 5yRS for clinical stage I tumours is 54%, but decreases to 26% in stage II, 17% in stage III and 2% in stage IV. Also, the histological subtype influences survival, for AC only, overall 5yRS is 10.4% (95%CI [9.7;11.2]) versus 72.9% (95%CI [69.5;76.1]) for NEN only.

For the convention period 1/7/2019 – **31/12/2021** (last 6 months of 3-year convention not yet available), 6.550 patients were diagnosed with peri-pancreatic cancer and notified through the cancer registration in the BCR database. Because of the limited follow-up time, survival results are limited to 1 year survival.

For the total Belgian malignant peri-pancreatic cancer cohort, overall observed 1 year survival (1yOS) was 45.8% 95%CI [44.6, 47.0]. According to the stage at diagnosis, for clinical stage I tumours 1yOS was 73%, but decreases to 61% in stage II, 53% in stage III and 25% in stage IV.

Important remark: The following survival analyses in this report will focus on *adenocarcinoma only* (see Table 1 below). Also, death *by all causes* is reported.

1. Unadjusted observed survival 1 year after surgery for patients with adenocarcinoma discussed on MC expert and **selected for surgery**

For the following analyses, 1yOS will be assessed after the *date of surgery* (not after date of diagnosis).

a. Description average results for surgery during the convention

Overall 1yOS for patients operated for primary adenocarcinoma of the peri-pancreas in the convention (N=1.553, all surgeries) was 75.3% 95%CI [72.9, 77.5]. According to the stage at diagnosis, for clinical stage I adenocarcinoma 1yOS was 78%, but decreases to 70% in stage II and 75% in stage III. The 1yOS for stage IV could not be determined because there weren't enough diagnoses.

b. Comparison of average convention results for *all operated primary adenocarcinoma* with average $T0_{(2015\text{-}2018)}$ results

Overall 1yOS for the $T0_{2015\text{-}2018}$period (N=1.826$_{(adenocarcinoma\ only)}$) was 72.2% 95%CI [70.1, 74.2]. According to the stage at diagnosis, for clinical stage I adenocarcinoma $T0_{2015\text{-}2018}$ 1yOS was 76%, but decreases to 68% in stage II and III, and 51% in stage IV.

2. Unadjusted observed survival 1 year after diagnosis of patients with adenocarcinoma discussed on MC expert but **not selected for surgery**

For the following analyses, 1yOS will be assessed after the *date of diagnosis*.

a. Description average results during the convention (all primary adenocarcinoma discussed on MC and no surgery)

Overall survival 1 year *after diagnosis* for the convention (N=1.752) was 41.8% 95%CI [39.3, 44.2]. According to the stage at diagnosis, for clinical stage I adenocarcinoma 1yOS was 45%, 51% in stage II and II and 34% in stage IV.

b. Comparison of average 1yOS during the convention for patients with primary adenocarcinoma treated with or without surgery

Overall survival 1 year *after diagnosis* for patients operated for primary adenocarcinoma of the peri-pancreas in the convention period (N=1.552, all surgeries) was 79.7% 95%CI [77.5, 81.7], compared with 41.8% 95%CI [39.3, 44.2] for the patients with primary adenocarcinoma that were discussed but not selected for surgery (see Table 1 below).

3. Unadjusted observed survival 1 year after diagnosis of patients with adenocarcinoma that were **not discussed on MC expert**

For the following analyses, 1yOS will be assessed after the *date of diagnosis*.

Description average results during the convention period (all patients not discussed on MC expert)

Overall 1yOS for the convention period [1/7/2019 – 31/12/2021] (patients with adenocarcinoma not discussed on MC, N=2.220) was 26.6% 95%CI [24.8, 28.4]. According to the stage at diagnosis, for clinical stage I adenocarcinoma 1yOS was 45%, and decreases to 33% in stage II, 40% in stage III and 22% in stage IV (see Table 1 below).

Table 1 - Overview of the unadjusted 1-year OS for the different subgroups of patients with peri-pancreatic adenocarcinoma, all calculated after date of diagnosis

	T0$_{2015-2018}$period		**Convention period**			
	T0$_{2015-2018}$period All primary peri-pancreatic AC	**T0$_{2015-2018}$period** With surgery*	**[1/7/2019 – 31/12/2021]** All primary peri-pancreatic AC	**[1/7/2019 - 30/06/2022]** With surgery*	**[1/7/2019 - 30/06/2022]** No surgery	**[1/7/2019 – 31/12/2021]** Not discussed on MC
Overall 1yOS	41% (N=6824)	75% (N=1826)	44% (N=4859)	80% (N=1552)	42% (N=1752)	27% (N=2220)
cStage I	68% (N=642)	79% (N=434)	70% (N=858)	81% (N=743)	45% (N=205)	45% (N=129)
cStage II	54% (N=781)	73% (N=374)	60% (N=625)	76% (N=445)	51% (N=226)	33% (N=131)
cStage III	49% (N=479)	72% (N=94)	57% (N=498)	83% (N=163)	51% (N=332)	40% (N=127)
cStage IV	22% (N=2690)	55% (N=49)	26% (N=2130)	- (N=30)	34% (N=901)	22% (N=1361)

* Calculated from date of diagnosis

1yOS by clinical stage is only provided if clinical stage information is available (so not provided for clinical stage unknown or not applicable).

Proportion of surgically treated patients with resection margin R0, R1, R2 (only for pancreatic ductal adenocarcinoma)

In the convention database, data were collected on radicality of the resection. The rate of R0 resections is regarded as an important prognostic factor in oncological surgery. Nevertheless, in the literature, controversy exists regarding the definition of R0 and R1 after pancreatic surgery.[6]

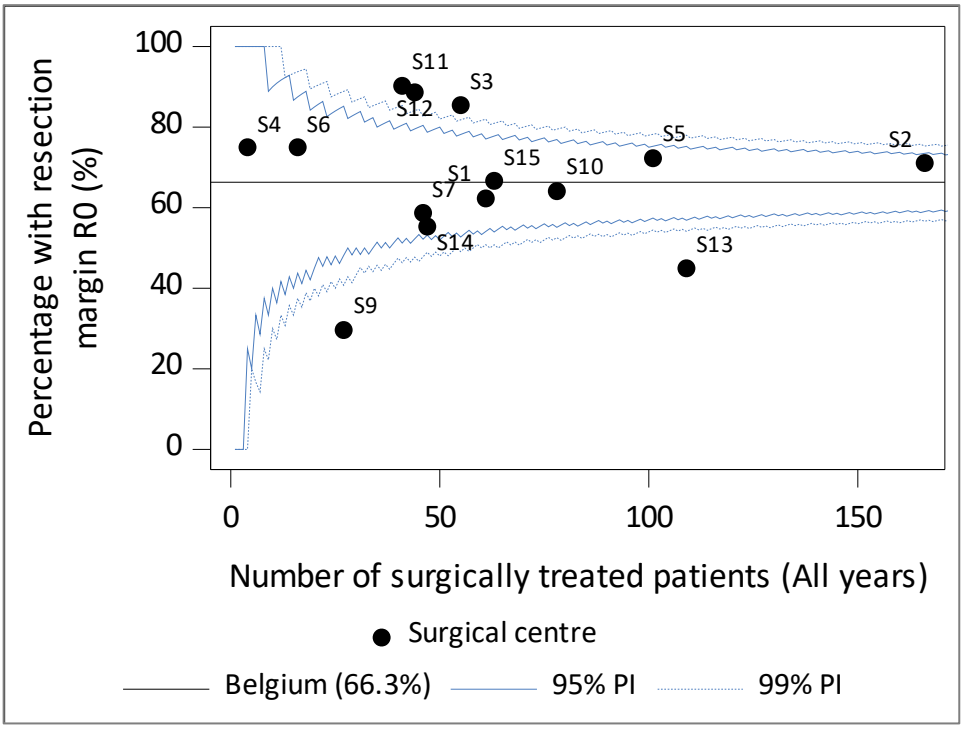
During the course of the convention, repetitive remarks and concerns were raised by the clinical experts concerning the heterogeneity between the centres as for the pathological evaluation of the resection specimens. The use of similar guidelines to examine the resection specimen was doubted, and the definition of R1 and the distinction of R1 direct/indirect were matter of debate.

For the indicators on the resection margin, it was requested to limit the denominator to the *ductal adenocarcinoma of the pancreas only* (ICD-0-3 topography C25 and morphology 8500). Therefore, the numbers are much lower than the total number of surgeries (N=858). Also, some centres did not use the appropriate morphology code, and thus they had very low numbers of cases to evaluate.

Description average results for the convention period and centre specific results *(Appendix F)*

a) Proportion resected ductal adenocarcinoma of the pancreas with R0

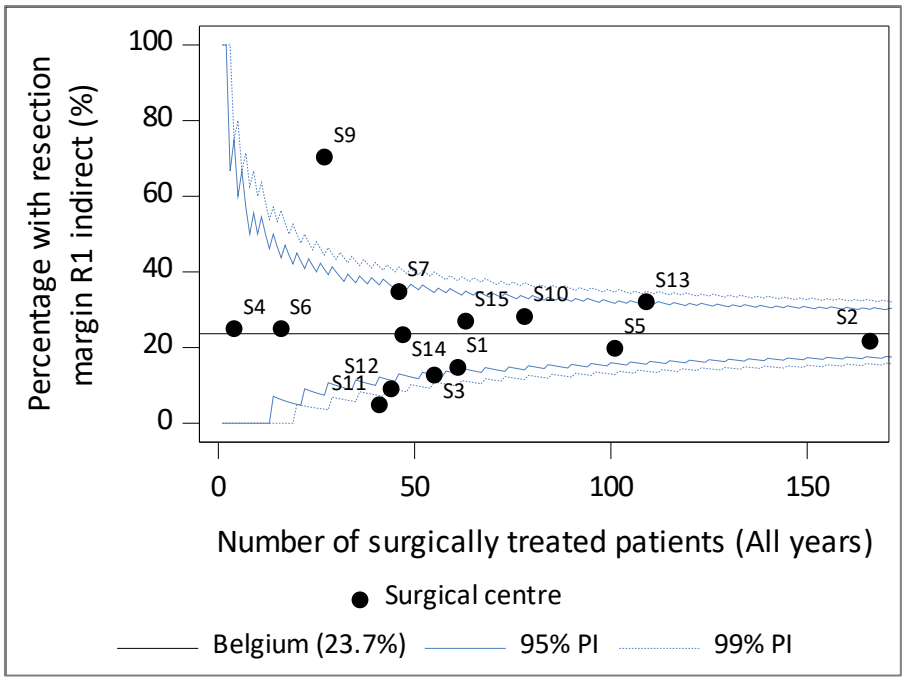
Of the 858 patients with resected ductal adenocarcinoma of the pancreas, 569 (66.3%) was found to be R0.



Note: 1 hospital could not be displayed because it had no cases for the current selection.

b) Proportion resected ductal adenocarcinoma of the pancreas with R1indirect

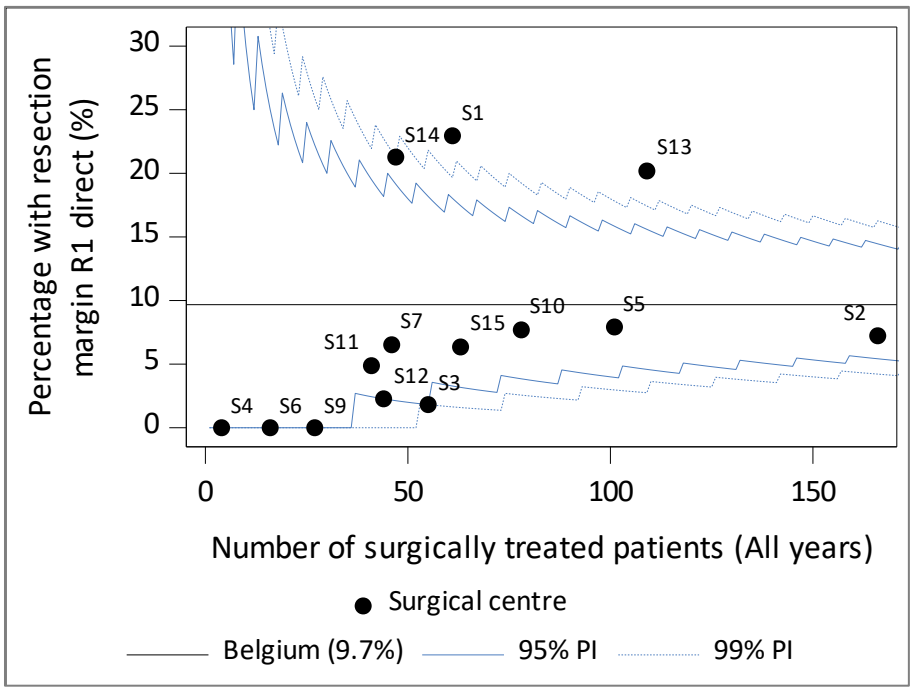
Of the 858 patients with resected ductal adenocarcinoma of the pancreas, 203 (23.7%) was found to be R1indirect.



Note: 1 hospital could not be displayed because it had no cases for the current selection.

c) Proportion resected ductal adenocarcinoma of the pancreas with R1direct

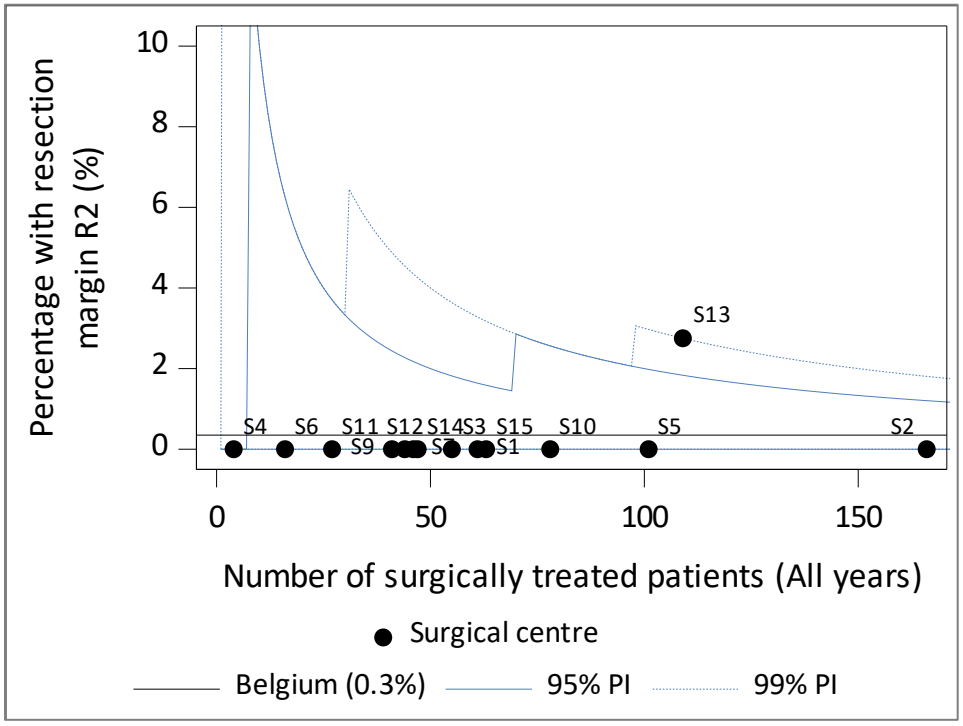
Of the 858 patients with resected ductal adenocarcinoma of the pancreas, 83 (9.7%) was found to be R1direct.



Note: 1 hospital could not be displayed because it had no cases for the current selection.

d) Proportion resected ductal adenocarcinoma of the pancreas with R2

Of the 858 patients with resected ductal adenocarcinoma of the pancreas, 3 (0.3%) was found to be R2.



Note: 1 hospital could not be displayed because it had no cases for the current selection.

Postoperative complications (malignant + benign tumours)

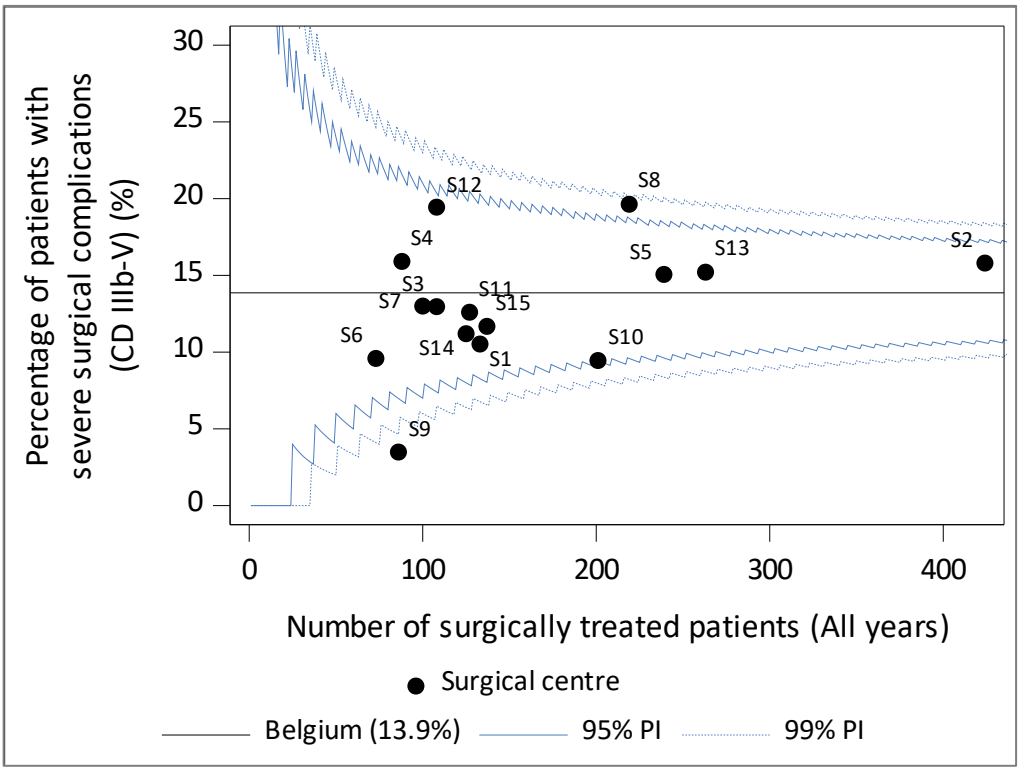
Pancreatic surgery is associated with significant morbidity and mortality. According to the literature overall morbidity remains high, with reported rates up to 60%.[7,8] For the convention, complications were rated using the Clavien-Dindo (CD) and the International Study Group of Pancreatic Surgery (ISGPS) classification systems.

Remark: Although it was defined which classifications systems were to be used to rate the complications, concerns were raised by the clinical experts as for the reliability of the registration of complications within the convention.

Description average results for the convention and centre specific results *(Appendix F)*

Severe surgical complications in general, pancreatic fistula, haemorrhage, delayed gastric emptying, bile leakage and intra-abdominal abscess were documented separately *(Appendix D – global 3-year report)*.

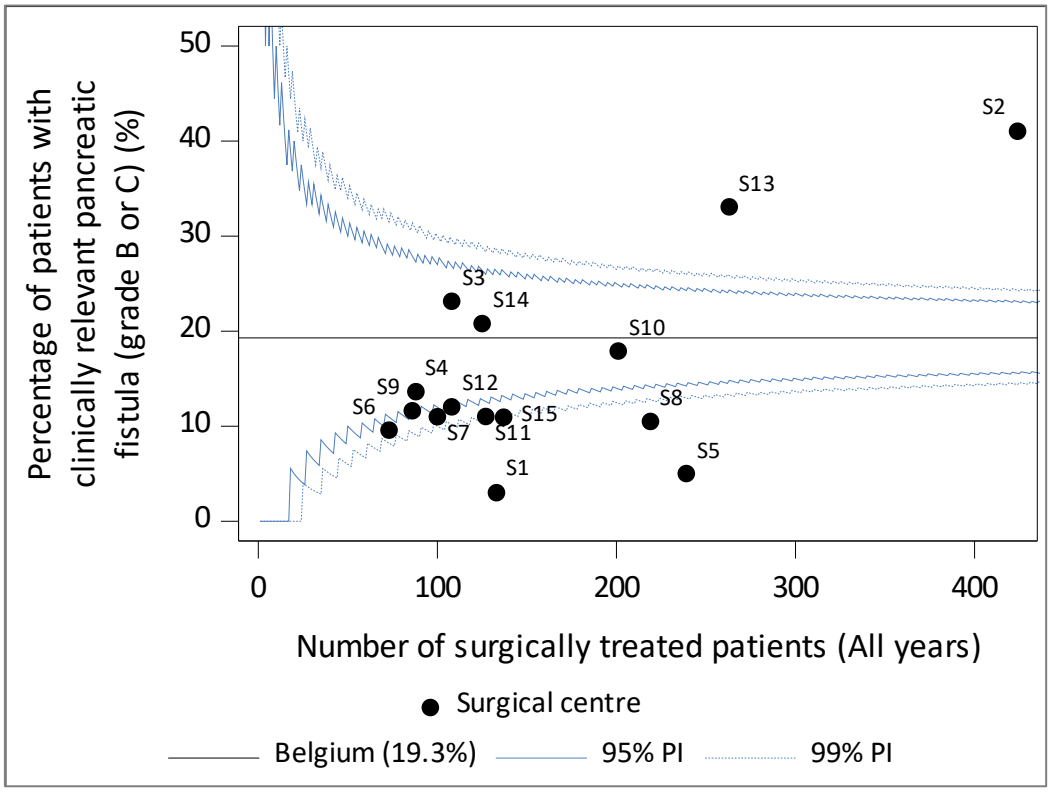
a) Severe surgical complications



Severe surgical complications were defined CD ≥IIIb. On average, in about 14% of the cases, severe surgical complications were documented, an overall result that was consistent over the 3 years. Appendix D provides more details on the patient/tumour/treatment characteristics associated with severe complications. The % of severe complications ranged between 3.5% and 19.6% among the different centres.

b) Clinically relevant pancreatic fistula

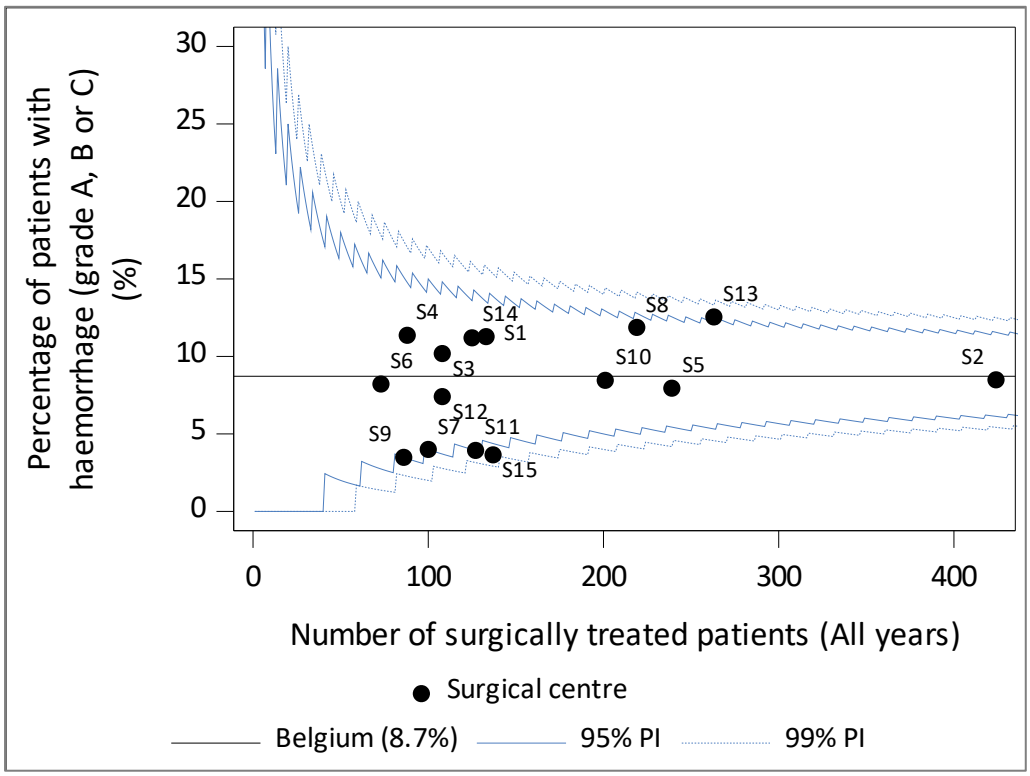
Postoperative pancreatic fistula is reported in the literature as the most common complication after pancreatic surgery, the reported rates ranging between 2% to 20% in high-volume centres.[9] During the 3 convention years, clinically relevant pancreatic fistula (ISGPS Grade B or C) was registered in 19% of the cases.



Results for pancreatic fistula Grade B and C separately on centre level can be found in Appendix D.

c) Haemorrhage

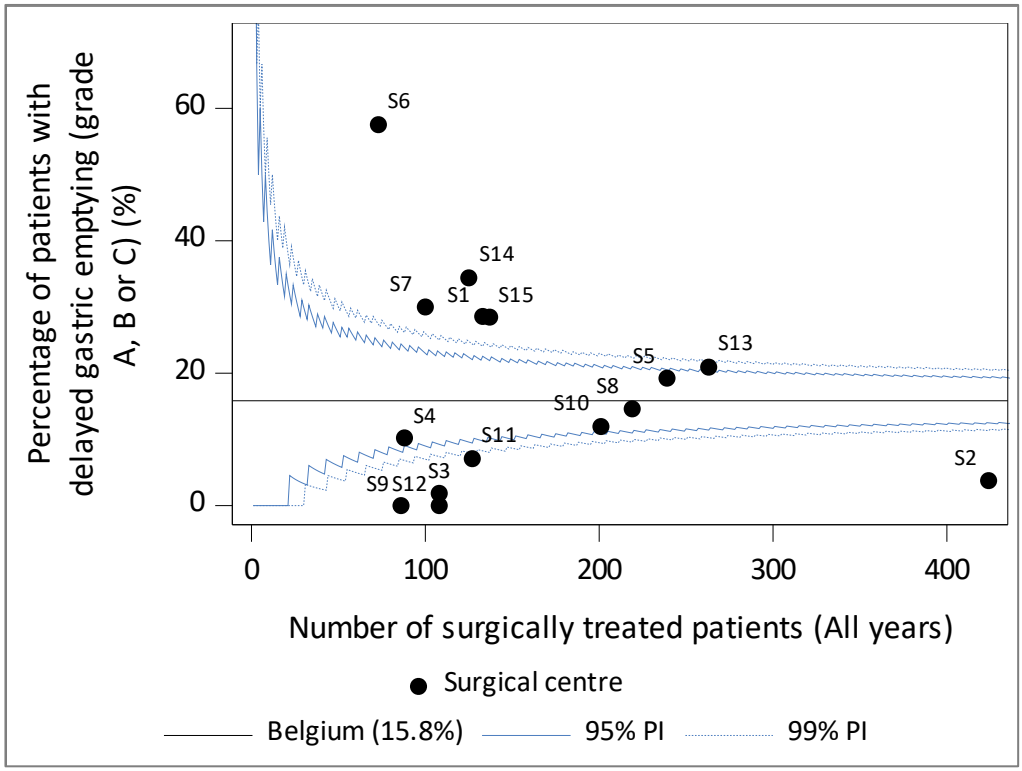
According to the literature, reported rates of postpancreatectomy haemorrhage range between 1% and 8%.[10] In the convention data, haemorrhage ISGPS Grade A, B or C was registered in 9%.



Separate results for haemorrhage Grade B and C on centre level can be found in Appendix D.

d) Delayed gastric emptying

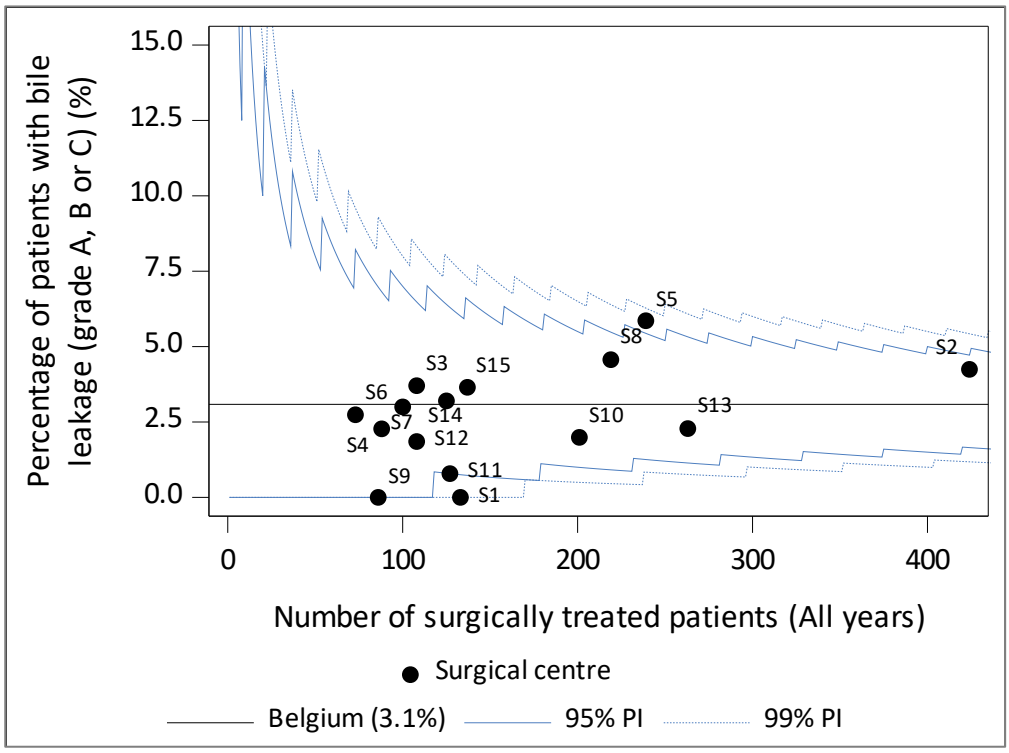
Rates ranging between 19% and 57% are reported in the literature as for delayed gastric emptying.[11] The registered rate of delayed gastric emptying ISGPS Grade A, B or C, in the convention was 16%.



Separate results for delayed gastric emptying Grade B and C on centre level can be found in Appendix D.

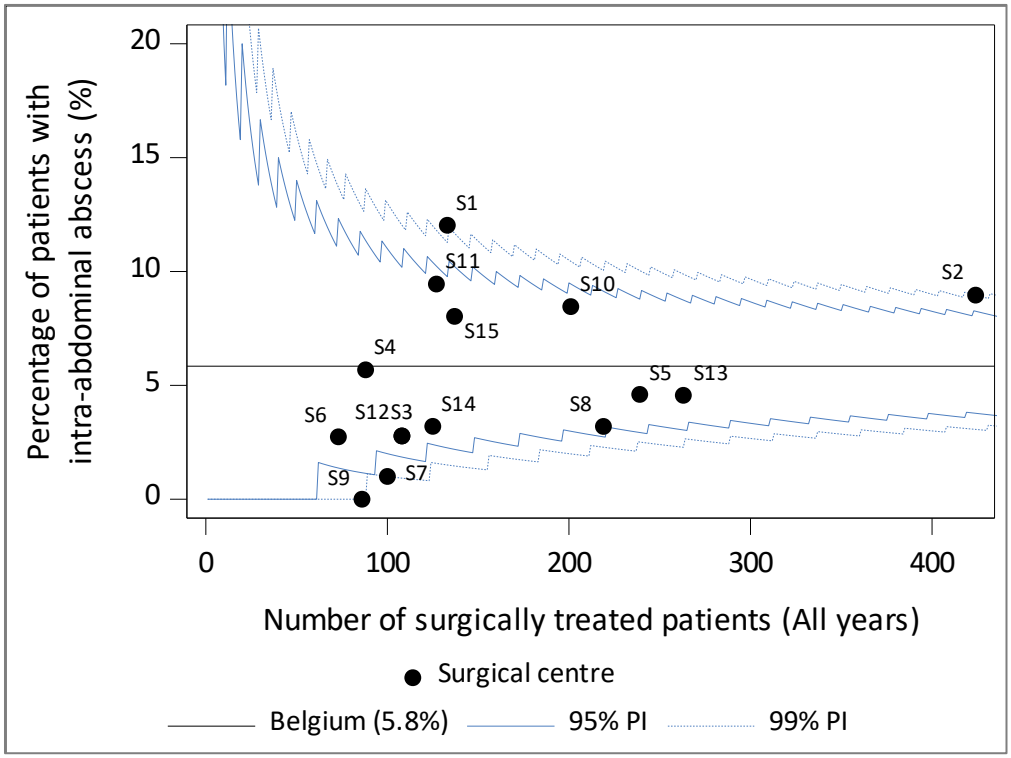
e) Bile leakage

Registered bile leakage ISGPS Grade A, B or C in the convention was 3%.



Separate results for bile leakage Grade B and C on centre level can be found in Appendix D.

f) Intra-abdominal abscess



Intra-abdominal abscess was registered in 6% of the cases in the convention.

Evaluation individual organization of care in expert centres

Appendix F provides an overview of several results **on hospital level**.

Volume criteria

An important pillar of the convention, aiming at quality-of-care improvement, was the structural condition of a minimal surgical volume for each individual expert centre. The imposed minimal volume after the three-year period was 75 pancreatic procedures and was reached by all 15 expert centres. Together with a minimal surgical volume, a minimal volume of specialized multidisciplinary meetings was determined, i.e. 120 discussions after three years. All 15 centres reached the minimal volume of discussions.

Time to treatment

The median time that passed between the histological confirmation of adenocarcinoma and the start of any first treatment (options regarded as first treatment being chemotherapy, radiotherapy or surgery) for the patients treated in T0 was 17 days (IQR 0-30), compared to 19 days (IQR 0-33) for the patients treated in the convention. This slight increase in time to treatment for patients with adenocarcinoma requires attention, analysis could not reveal a difference in time to treatment between patients that were referred and those that presented immediately at the expert centre. Nevertheless 4/15 expert centres had a median time to first treatment of an adenocarcinoma that was at least 5 days longer than the overall median result of 25 days.

Differences in individual performance of the 15 expert centres

The median age and M/F ratio of the surgically treated patients varied between the different centres, the highest median age being 72 years, and the highest M/F ratio being 2.1. The distribution between AC and NEN was comparable among all centres, as was patient selection for surgery regarding tumour indication (primary/recurrence/metastasis). The proportion of Whipple surgeries (pancreaticoduodenectomies) varied between the centres from 52% to 83% of all procedures, the proportion of enucleations was similar. Important variation was noted between the individual centres regarding the applied surgical technique, open versus minimally invasive, also the type of minimal invasive surgery varied (laparoscopic versus robotic or hybrid). The overall 30-day postoperative mortality in patients with benign or malignant peri-pancreatic tumours was 2.4% (95%CI [1.9, 3.1]) (59 deaths over 2.431). The individual results, adjusted for the case mix of the different expert centres, showed a significantly higher 30-day mortality in 2 centres compared with the average. The overall 90-day postoperative mortality in patients with benign or malignant peri-pancreatic tumours was 5.1% (95%CI [4.3, 6.1]) (125 deaths over 2.431), the adjusted results showed a significantly higher 90-day mortality in 1 centre – a different centre from the 2 centres that deviated for their 30-day postoperative mortality - compared with the average, and also a significantly lower 90-day mortality in 2 expert centres compared with the average. Based on the adjusted mortality results, all other 10 centres performed comparable.

General commitment contributing to a continuous system of quality improvement

All expert centres attended to meetings that were organized by the RIZIV-INAMI to discuss the annual results. The centres also annually prepared an individual evaluation with the formulation of concrete action points for their own centre. Finally, the 15 expert centres united their scientific interests and created a new scientific group named Belgian Pancreatic Cancer Group (BPCG). The BPCG gathered at regular times to discuss specific surgery-related topics, to exchange experiences and to propose new research questions. For the continuation of the convention, the BPCG can play an important role in the process of continuous quality improvement.

Reflections and recommendations based on evaluation after 3 years

- A standardized protocol for the anatomopathologist to evaluate the resection margin status of the pancreaticoduodenectomy specimen is necessary to allow comparison of the results.
- Uniform guidelines on the pathological evaluation of removed lymph nodes during surgery are necessary to allow comparison of these data.
- The evaluation of postoperative complications by registrars needs to be trained to achieve uniform interpretation.
- A substantial proportion of the patients diagnosed with pancreatic cancer during the 3-year period was not discussed on a specialized MC in an expert centre (more than 40%). For the continuation of the convention, this population needs to be characterized further to evaluate whether it is recommended to organize a specialized MC for every patient with newly diagnosed pancreatic cancer.
- Data regarding patient experience and quality of life were not collected, this should be considered for the continuation of the convention.
- Data regarding recurrences were not collected, this should be included in the future.

Addendum: observed mortality year 4 of the convention

The evaluation report is based on collected data from 1 July 2019 until 30 June 2022. Awaiting the in depth-analysis of the subsequent year (1/7/2022 until 30/6/2023), the observed 90-day mortality results of the fourth year were already computed.

The observed 90-day postoperative mortality for malignant peri-pancreatic cancer during the subsequent convention years evolved from 5.3% (year 1), to 5.8% (year 2), 5.7% (year 3) and finally 3.7% in year 4. With the addition of the fourth convention year, the 90-day postoperative mortality was assessed for a total of $N_{4Yconvention}$=2.684 and compared with $N_{T0\ 2015-2018}$=2.261. Thereby, the overall unadjusted 90-day postoperative mortality for four years of convention is 5.1% 95%CI [4.3, 6.0] compared to 7.3% 95%CI [6.3, 8.4] for the four years preceding the centralization of pancreatic surgery, and confirms the decreasing trend.

References

1. Peacock HM, Tambuyzer T, Verdoodt F, et al. Decline and incomplete recovery in cancer diagnoses during the COVID-19 pandemic in Belgium: a year-long, population-level analysis. ESMO Open. 2021 Aug;6(4):100197. doi: 10.1016/j.esmoop.2021.100197. Epub 2021 Jun 11. PMID: 34474811; PMCID: PMC8411068.
2. Allemani, C. C., Matsuda, T. T., Di Carlo, V. V., et al. (2018). Global surveillance of trends in cancer survival: analysis of individual records for 37,513,025 patients diagnosed with one of 18 cancers during 2000–2014 from 322 population-based registries in 71 countries (CONCORD-3). *The Lancet (British Edition)*, *391*(10125), 1023–1075. https://doi.org/10.1016/S0140-6736(17)33326-3
3. Strobel O, Hinz U, Gluth A, et al. Pancreatic adenocarcinoma: number of positive nodes allows to distinguish several N categories. Ann Surg. 2015;261:961–9.
4. Schwarz RE, Smith DD. Extent of lymph node retrieval and pancreatic cancer survival: information from a large US population database. Ann Surg Oncol 2006;13(9):1189–1200
5. Gonzalez RS. Staging-exocrine. PathologyOutlines.com website. https://www.pathologyoutlines.com/topic/pancreastnm.html. Accessed June 27th, 2023.
6. Strobel O, Hank T, Hinz U, et al. Pancreatic Cancer Surgery: The New R-status Counts. Ann Surg. 2017 Mar;265(3):565-573. doi: 10.1097/SLA.0000000000001731. PMID: 27918310
7. Dusch N, Lietzmann A, Barthels F, et al. International Study Group of Pancreatic Surgery Definitions for Postpancreatectomy Complications: Applicability at a High-Volume Center. Scand J Surg. 2017 Sep;106(3):216-223. doi: 10.1177/1457496916680944. Epub 2017 Apr 4. PMID: 28376656.
8. Beal, E. W. (2022). Algorithm-based management of complications after pancreatic resection. *The Lancet (British Edition)*, *399*(10338), 1846–1847. https://doi.org/10.1016/S0140-6736(22)00626-2
9. Bassi C, Dervenis C, Butturini G, et al: Postoperative pancreatic fistula: An international study group (ISGPF) definition. Surgery 2005;138(1):8–13
10. Wente MN, Veit JA, Bassi C, et al: Postpancreatectomy hemorrhage (PPH): An International Study Group of Pancreatic Surgery (ISGPS) definition. Surgery 2007;142(1):20–25
11. Wente MN, Bassi C, Dervenis C, et al: Delayed gastric emptying (DGE) after pancreatic surgery: A suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). Surgery 2007;142(5):761–768