Journal of Gastrointestinal Surgery (2018) 22:1557–1564
https://doi.org/10.1007/s11605-018-3792-z

ORIGINAL ARTICLE

Natural History of Gas Configurations and Encapsulation in Necrotic Collections During Necrotizing Pancreatitis

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Received: 15 January 2018 / Accepted: 1 March 2018 / Published online: 11 May 2018

Abstract

Background Decision-making on invasive intervention in patients with clinical signs of infected necrotizing pancreatitis is often related to the presence of gas configurations and the degree of encapsulation in necrotic collections on imaging. Data on the natural history of gas configurations and encapsulation in necrotizing pancreatitis are, however, lacking.

Methods A post hoc analysis was performed of a previously described prospective cohort in 21 Dutch hospitals (2004–2008). All computed tomography scans (CTs) performed during hospitalization for necrotizing pancreatitis were categorized per week (1 to 8, and thereafter) and re-assessed by an abdominal radiologist.

Results A total of 639 patients with necrotizing pancreatitis were included, with median four (IQR 2–7) CTs per patient. The incidence of first onset of gas configurations varied per week without a linear correlation: 2–3–13–11–10–19–12–21–12%, respectively. Overall, gas configurations were found in 113/639 (18%) patients and in 113/202 (56%) patients with infected necrosis. The incidence of walled-off necrosis increased per week: 0–3–12–39–62–76–93–97–100% for weeks 1–8 and thereafter respectively. Clinically relevant walled-off necrosis (largely or fully encapsulated necrotic collections) was seen in 162/379 (43%) patients within the first 3 weeks.

Conclusions Gas configurations occur in every phase of the disease and develop in half of the patients with infected necrotizing pancreatitis. Opposed to traditional views, clinically relevant walled-off necrosis occurs frequently within the first 3 weeks.

Keywords Necrotizing pancreatitis · Gas configurations · Encapsulation

Janneke van Grinsven and Sandra van Brunschot contributed equally to this work.

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Introduction

Acute pancreatitis is the most common gastrointestinal disorder requiring hospital admission in the USA and its incidence is rising.[1] Necrotizing pancreatitis, defined as necrosis of the pancreatic parenchyma and/or extrapancreatic fat tissue, occurs in around 20% of patients.[2,3] Associated collections in necrotizing pancreatitis (necrotic collections) are either called "acute necrotic collections" (not fully encapsulated) or "walled-off necrosis" (fully encapsulated).[4] In case of infected necrosis, an invasive intervention is nearly always needed.[5,6] Current guidelines advise a step-up approach in patients with infected necrosis, starting with catheter drainage. If the patient does not recover with drainage alone, minimally invasive necrosectomy is performed.[5,6] Although overall outcome has improved over the last decade, mortality and morbidity in these patients are still 15 and 40%, respectively.[7]

Decision-making on invasive intervention is influenced by clinical, biochemical, and imaging features, primarily on

computed tomography (CT). Two CT features stand out in the decision-making process. First, the presence of gas configurations within necrotic collections is deemed important as this is regarded pathognomonic for infected necrosis. Second, the degree of encapsulation of necrotic collections is relevant because drainage is typically postponed until necrotic collections are largely or fully encapsulated. The timing of invasive intervention in patients with infected necrotizing pancreatitis, however, remains a topic of debate.[8]

It is often assumed that gas configurations occur most often between the second and fourth week and that full encapsulation of necrotic collections occurs at least 4 weeks after symptom onset. Accurate data supporting these statements are, however, lacking.[4] Improved knowledge about the natural course of necrotic collections might support decision-making on the timing of invasive intervention. Moreover, it can add to the interpretation and further standardization of clinical research in necrotizing pancreatitis.

The main purpose of this study was to evaluate the natural history of gas configurations in and encapsulation of necrotic collections on CT during the disease course of necrotizing pancreatitis. In addition, clinical and radiological factors associated with occurrence of gas and (early) encapsulation in necrotic collections were studied.

Methods

Study Design and Patients

This study is a post hoc analysis of a prospective cohort of patients with necrotizing pancreatitis, collected from 2004 to 2008 in 21 Dutch hospitals of the Dutch Pancreatitis Study Group.[9] All contrast-enhanced CTs performed during the index admission and before any kind of invasive (surgical, endoscopic, or percutaneous) intervention were re-assessed by an experienced abdominal radiologist (TLB). Patients with at least one CT confirming the diagnosis of necrotizing pancreatitis were included. Follow-up CTs were performed in case of a lack of clinical improvement according to current standard practice. CTs after any intervention were excluded. CTs were collected from all participating hospitals (including referral hospitals in transferred patients). Different brands of CT scanners were used and CT protocols varied widely among hospitals, varying from a monophasic to four-phasic CT protocol. All CTs, however, were executed with a multislice technique (at least a 16-slice multidetector CT scanner or higher) with 3-mm reconstructions and were contrast-enhanced in the pancreatic and/or portal venous phase. Also, in most cases, reformatted images were available for review. Non-invasive treatment consisted of intravenous fluid therapy, oral or enteral feeding, and adequate pain management. Invasive interventions were performed in cases of (suspected) infected necrosis based on gas configurations on CT, positive culture after fine needle aspiration, or clinical deterioration with no other cause than infected necrosis.[10]

Data Extraction

All CTs were categorized into groups according to duration since onset of disease, i.e., weeks 1 to 8, and further. If more than one CT was performed in a week, the last CT was used for assessment. In all CTs, the presence of first onset of gas configurations was evaluated (see Fig. 1a, b for CT examples). Gas configurations depicted on every follow-up CT in patients undergoing a non-invasive treatment were not scored in the incidence assessment. The degree of encapsulation was scored as none (0%), moderately (less than 50%), largely (between 50 and 99%), or fully (100%) encapsulated (see CT examples in Fig. 2a–d). Walled-off necrosis was defined according to the Revised Atlanta Classification as fully encapsulated necrotic collections.[4] In clinical practice, however, invasive intervention is contemplated and deemed feasible when infected

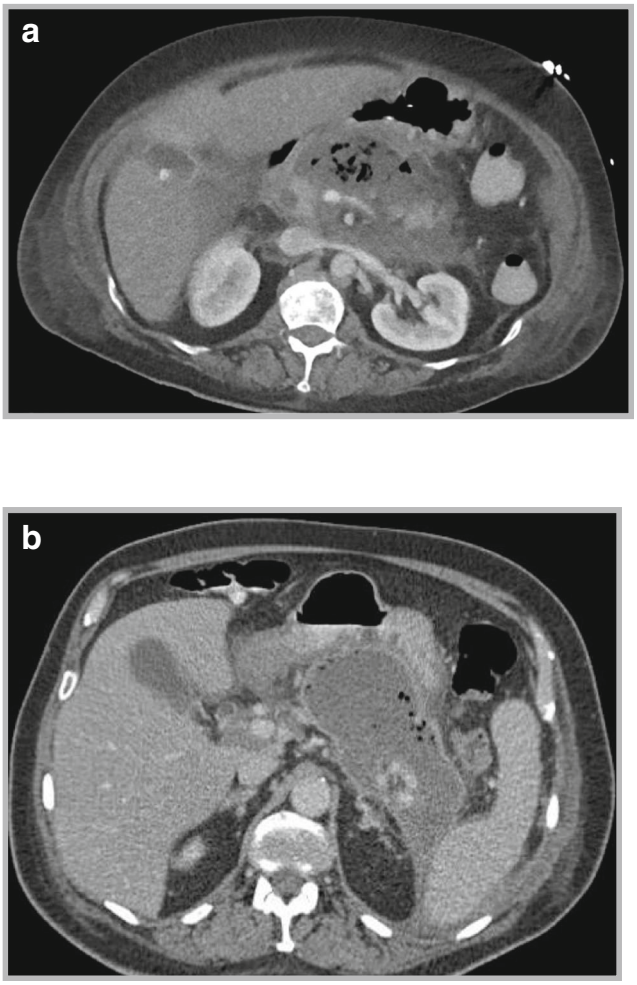


Fig. 1 **a** CT with gas configurations in acute necrotic collection. **b** CT with gas configurations in walled-off necrosis

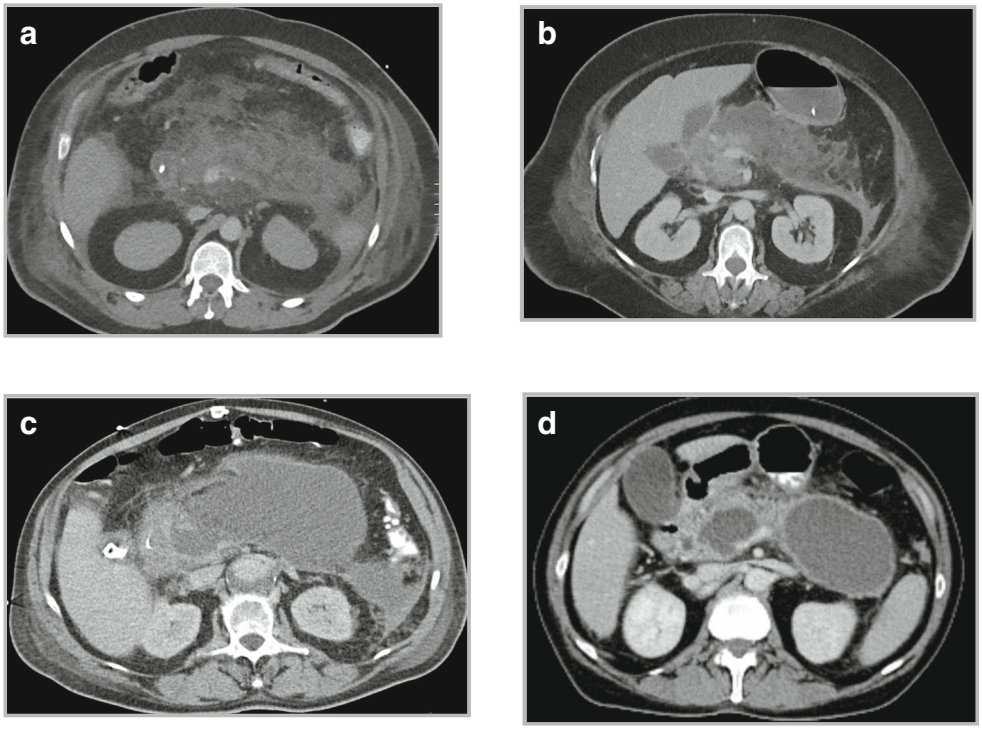


Fig. 2 **a** CT (1) not encapsulated (0%). **b** CT (2) moderately encapsulated (< 50%). **c** CT (3) largely encapsulated (50–99%). **d** CT (4) fully encapsulated/walled-off necrosis (100%)

necrotic collections are largely or fully encapsulated. Hence, besides the original definition of walled-off necrosis, we also assessed a more clinically relevant definition of walled-off necrosis, defined as necrotic collections that are largely or fully encapsulated. In this line of reasoning, we defined "early walled-off necrosis" as largely or fully encapsulated collections occurring within 3 weeks after symptom onset, i.e., before the traditional 4 weeks mentioned in the Revised Atlanta Classification.[4] The following clinical baseline data were available: age, sex, disease etiology, and American Society of Anesthesiologists (ASA) classification. Data on type and timing of intervention and clinical outcome in patients with suspected infected necrosis have been published previously.[9,10]

Statistical Analysis

Data were analyzed using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA). Outcomes were reported as absolute numbers and percentages for categorical variables. Continuous variables were summarized as either means with corresponding standard deviations (SD) or medians with interquartile ranges (IQR) depending on normality of distribution. Univariable logistic regression was performed to identify factors associated with the occurrence of gas configurations and for "early walled-off necrosis". Factors associated in the univariable analysis ($P < 0.1$) were entered into a multivariable logistic regressions analysis (backward stepwise elimination method). A two-sided P value below 0.05 was considered statistically significant for all statistical tests.

Results

The study cohort consisted of 639 patients with necrotizing pancreatitis. Median age was 58 years (IQR 45–70) and 62% (398) of patients were male. A median of four (IQR 2–7, range 1–23) CTs was performed per patient (Table 1). The median CT severity index was 4 (IQR 4–8). In 324 (51%) patients, pancreatic parenchymal necrosis was present; in the remainder of 315 (49%) patients, there was extrapancreatic necrosis only. A median of three (IQR 2–5) necrotic collections were observed per patient, mostly centrally located (i.e., predominantly in the lesser sac and/or transverse mesocolon) or left-sided (i.e., predominantly at the left side of the retroperitoneum), in 235 (37%) and 188 (29%) of patients, respectively. Figure 3 depicts the frequency per location of the (extra)pancreatic necrotic collections.

Gas Configurations

In 18% of patients (113 of 639 patients) and in 56% of patients with proven infected necrosis (113 of 202 patients), gas configurations were seen at some point in time. Figure 4 shows the number of patients (in percentage) in whom first onset of gas configurations was seen on CT per week: w1, 2%; w2, 3%; w3, 13%; w4, 11%; w5, 10%; w6, 19%; w7, 12%; w8,

Table 1 Clinical and radiological characteristics of 639 patients with necrotizing pancreatitis

	All patients (n = 639)
Age (years)	58 (45–70)
Male sex (%)	398 (62)
Etiology (%)	
Biliary	304 (48)
Alcohol	150 (23)
Other	63 (10)
Unknown	122 (19)
ASA classification on admission (%)	
I (healthy status)	202 (32)
II (mild systemic disease)	347 (54)
III (severe systemic disease)	90 (14)
No. of CTs per patient	
Total	4 (2–7)
Before intervention	3 (2–4)
CT severity index^	4 (4–8)
Pancreatic necrosis (%)	324 (51)
Extrapancreatic necrosis alone (%)[#]	315 (49)
Extent of pancreatic necrosis (%) *n = 324*	
< 30%	132 (40)
30–50%	83 (26)
> 50%	109 (34)
No. of necrotic collections	3 (2–5)
Location of necrotic collections (%)	
Left	188 (29)
Right	55 (9)
Central	235 (37)
Bilateral	161 (25)
Gas configurations on CT (%)	
Total	113 (18)
Among 202 patients with infected necrosisAfter intervention	113 (56)

Continuous variables are provided as mean (± SD) or median (IQR) depending on normality of distribution

ASA American Society of Anesthesiologists, *CT* computed tomography

^CT severity index (scores 1–10)

[#] No pancreatic necrosis present

21%; and > w8, 12%. There was no linear correlation. In a multivariable analysis, age ($P < 0.001$), presence of pancreatic necrosis ($P < 0.001$), number of necrotic collections ($P = 0.018$), and left-sided collections ($P < 0.001$) were independently associated with the occurrence of gas configurations (see Table 2). As described previously, in 184 patients, infected necrosis was confirmed by culture taken at the first intervention.[10] In 114 of these 184 patients (62%), the infection was monomicrobial, whereas in 70 patients (38%), two or more bacteria/fungi were cultured. *Escherichia coli* was most frequently found in patients with gas bubbles on CT (42 patients), whereas in patients without gas bubbles, *Staphylococcus aureus* was most frequently found (34 patients). No single microorganism was found to be solely responsible for the formation of gas bubbles in necrotic collections.

Encapsulation

Figure 4 shows the degree of encapsulation related to the number of patients. The incidence of fully encapsulated necrotic collections (walled-off necrosis according to the Revised Atlanta Classification) increased per week: w1, 0%; w2, 3%; w3, 12%; w4, 39%; w5, 62%; w6, 76%; w7, 93%; w8, 97%; and > w8, 100%. Likewise, the incidence of largely or fully encapsulated necrotic collections (i.e., clinically relevant walled-off necrosis) increased per week: w1, 1%; w2, 17%; w3, 61%; w4, 88%; w5, 100%; w6, 99%; w7, 100%; w8, 100%; and > w8, 100%. Early clinically relevant walled-off necrosis (i.e., within the first 3 weeks) was seen in 162 of 379 (43%) patients. Male sex ($P = 0.035$), pancreatic necrosis ($P = 0.014$), and the presence of gas configurations ($P = 0.044$) were independently associated with the occurrence of early clinically relevant walled-off necrosis in a multivariable analysis (see Table 3).

Discussion

This study provides novel information on the natural history of imaging features of first onset of gas configurations and encapsulation in necrotizing pancreatitis. The main findings are that first onset of gas configurations and walled-off necrosis occur in nearly every phase of the disease, well before as after 4 weeks of symptom onset. Although walled-off necrosis becomes more prevalent with time, over 40% of patients already develop clinically relevant walled-off necrosis within the first 3 weeks of disease.

Gas in necrotic collections is thought to be caused by gas-forming bacteria or loss of integrity of the gastrointestinal tract.[5] Both are considered pathognomonic for infected necrosis. Infected necrosis is almost always an indication for invasive intervention since only a small subset (< 5%) of patients recover with antibiotic treatment only.[9] Little is known about risk factors for gas configurations at imaging or the timing of its occurrence. According to our study, gas configurations are seen in every phase of the disease, i.e., very early as well as late in the disease course. Gas configurations were more often seen in patients with higher age, parenchymal necrosis, multiple collections, and left-sided collections. The association between these factors and gas configurations remains speculative. It is conceivable that the translocation of bacteria is facilitated in the elderly and in cases where necrotic collections are in direct contact over a longer segment of the intestine. This latter phenomenon may be more pronounced in patients with parenchymal necrosis (i.e., more extensive

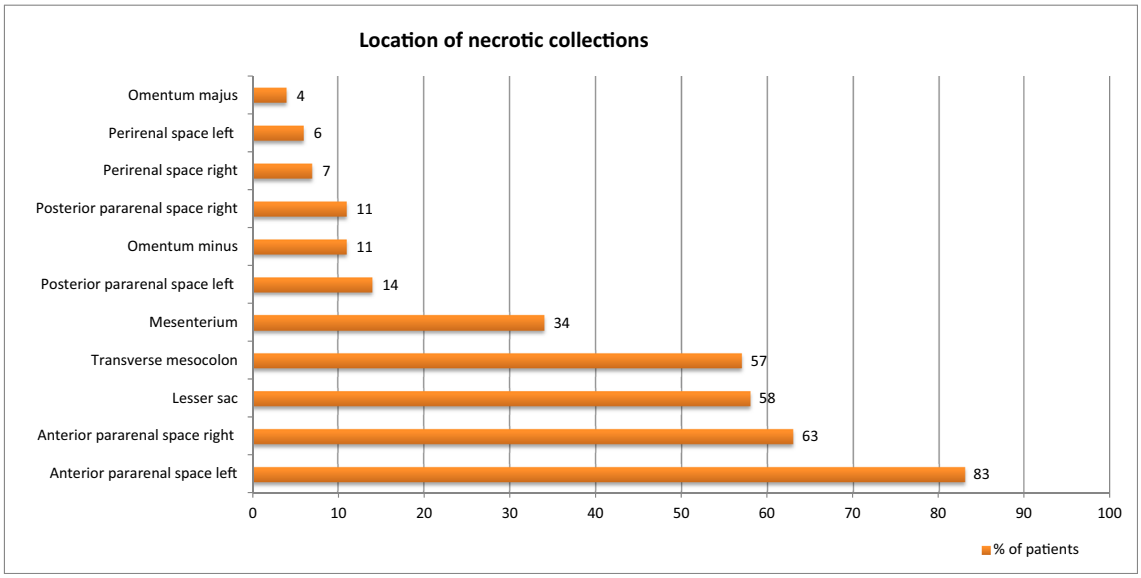
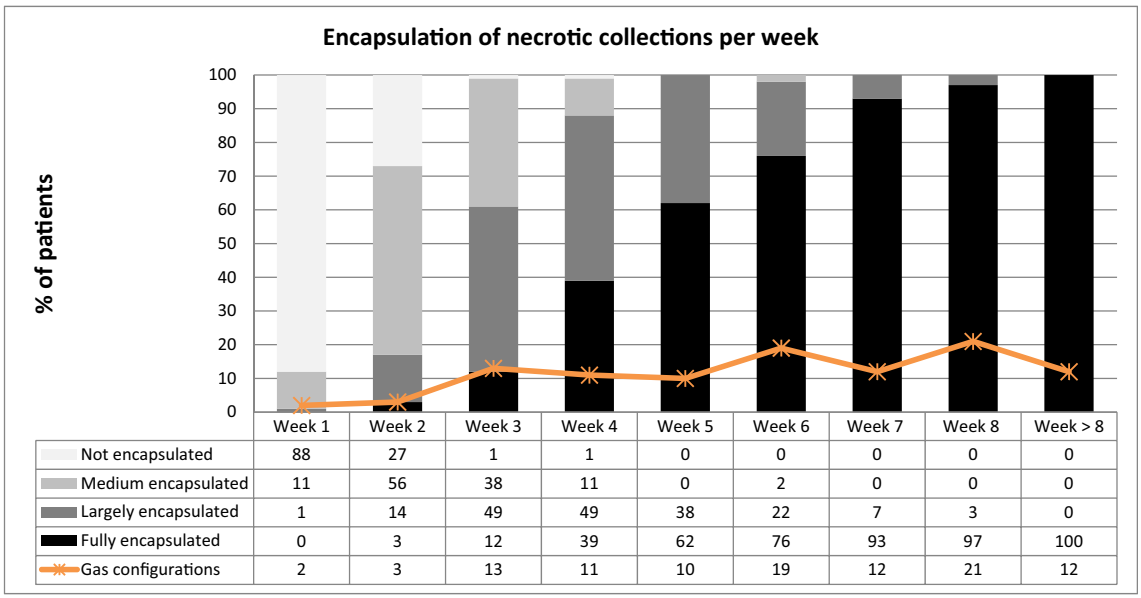


Fig. 3 Location of (extra)pancreatic necrotic collections in 639 patients, with a median of 3 (IQR 2–5) collections per patient

collections) and in those with multiple collections. Furthermore, the greater part of the pancreas is located left of the midline, which likely contributes to the preferential spread of necrotic collections to the left retroperitoneal compartment. More research on this topic is, however, required for verification of this association.

In the current study, different microorganisms were responsible for the occurrence of gas in necrotic collections, including Gram-positive and Gram-negative bacteria as well as yeasts. Also, in a significant number of patients, culture was polymicrobial. This justifies the institution of broad-spectrum antibiotics in patients with infected necrosis based on gas in necrotic collections, as routine narrowing of antibiotic treatment is not supported by our data.

The 2012 Revised Atlanta Classification classifies early pancreatic collections into acute peripancreatic fluid collections and acute necrotic collections that after 4 weeks develop into pancreatic pseudocysts and walled-off necrosis, respectively, when completely encapsulated.[4] Necrotic collections may involve the pancreatic parenchyma and/or extrapancreatic tissues and are considered a different clinical entity with a worse clinical outcome as compared with interstitial edematous pancreatitis.[4,11]



	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week > 8
Not encapsulated	88	27	1	1	0	0	0	0	0
Medium encapsulated	11	56	38	11	0	2	0	0	0
Largely encapsulated	1	14	49	49	38	22	7	3	0
Fully encapsulated	0	3	12	39	62	76	93	97	100
Gas configurations	2	3	13	11	10	19	12	21	12

Fig. 4 The degree of encapsulation and the presence of gas configurations in (extra)pancreatic necrotic collection per week. Only patients in whom CT was performed and (extra)pancreatic necrotic collections were seen (total $n = 639$ patients); first week $n = 540$ (85%); second week $n = 329$ (51%); third week $n = 195$ (31%); fourth week $n = 142$ (22%); fifth week $n = 87$ (14%); sixth week $n = 59$ (9%); seventh week $n = 43$ (7%); eighth week $n = 34$ (5%); beyond 8 weeks $n = 138$ (22%)

Table 2 Univariable and multivariable logistic regression analysis for factors associated with gas configurations (113 of 639 patients, 18%)

	Univariable OR (95% CI)	*P*	Multivariable OR (95% CI)	*P*
Age	1.019 (1.005–1.033)	*0.006*	1.032 (1.016–1.048)	*< 0.001*
Sex (male)	1.301 (0.846–2.001)	0.230		
ASA classification (ASA 3)	1.195 (0.681–2.095)	0.535		
CT severity index	1.309 (1.205–1.422)	*< 0.001*	0.986 (0.852–1.141)	0.852
Presence of pancreatic parenchymal necrosis	4.883 (2.994–7.964)	*< 0.001*	4.046 (2.398–6.826)	*< 0.001*
No. of necrotic collections	1.275 (1.152–1.410)	*< 0.001*	1.160 (1.026–1.312)	*0.018*
Location of necrotic collection (left vs. non-left)	3.499 (2.225–5.501)	*< 0.001*	2.780 (1.692–4.569)	*< 0.001*

Factors associated with $P<0.1$ in the univariable analysis were entered into the multivariable analysis. $P<0.05$ was considered statistically significant, *ASA* American Society of Anesthesiologists, *CT* computed tomography, *OR* odds ratio, *CI* confidence interval

Little is known about the natural history of imaging features of necrotic collections. Previous studies have evaluated the natural clinical history of (extra)pancreatic collections, but did not analyze their imaging characteristics or the timing of encapsulation.[12–15] Some have studied the clinical course (i.e., resolution) of pancreatic fluid collections and risk factors associated with the presence of pancreatic collections,[12,13] analyzed clinical and biochemical factors associated with formation of encapsulation (or "pseudocyst formation"),[12,14] or evaluated resolution of necrotic collections in the later phase of a disease by means of endoscopic ultrasound or transabdominal ultrasonography (i.e., not by CT) at different time points (i.e., after 4–6 weeks up to 6 months).[13,15]

The pathophysiology and rate of encapsulation of necrotic collections are as of yet incompletely understood. It is generally assumed that in necrotizing pancreatitis, the premature release of activated pancreatic enzymes and resultant acinar cell injury incites an extensive local and systemic inflammatory response. Locally, this might be regarded as a natural defense mechanism in which the body attempts to contain the area of inflammation. Over time, a capsule of granulation tissue is formed at the periphery to separate the inflamed tissue from healthy tissue to mitigate further spread of toxic enzymes and thus to wall off necrotic collections. This natural process of walling off an inflammatory process is likely analogous to an abscess wall formation. It is often stated (but not studied) that the timing of encapsulation takes about 4 weeks and this timescale is incorporated by the Revised Atlanta Classification. In the current study, however, there was a wide temporal range in which necrotic collections eventually became walled-off. In 85% of patients, it took well over 4 weeks for necrotic collections to become completely walled-off, whereas in 3 and 12%, complete encapsulation was already noted during the second and third weeks, respectively. Moreover, early clinically relevant walled-off necrosis (within the first 3 weeks) occurred in 43% and was more seen in male patients, patients with parenchymal necrosis, and patients with gas configurations (i.e., parameters associated with poorer clinical outcome).[16,17] The reason for the wide temporal range and observed associations with early encapsulation remains speculative. Possibly, the magnitude of inflammatory response incited locally together with immune-mediated and

Table 3 Univariable and multivariable logistic regression analysis for factors associated with early walled-off necrosis (i.e., within 3 weeks; 162 of 379 patients, 43%)

	Univariable OR (95% CI)	*P*	Multivariable OR (95% CI)	*P*
Age	1.004 (0.991–1.018)	0.522		
Sex (male)	0.655 (0.427–1.005)	0.053	0.625 (0.403–0.967)	*0.035*
ASA classification (ASA 3)	0.957 (0.536–1.707)	0.881		
CT severity index	1.062 (0.974–1.159)	0.173		
Presence of pancreatic parenchymal necrosis	1.852 (1.190–2.881)	*0.006*	1.761 (1.119–2.772)	*0.014*
No. of necrotic collections	1.019 (0.917–1.132)	0.730		
Location of necrotic collection (left vs. non-left)	1.233 (0.782–1.944)	0.368		
Gas configurations	1.762 (1.118–2.778)	*0.015*	1.617 (1.014–2.580)	*0.044*

Factors associated with $P<0.1$ in the univariable analysis were entered into the multivariable analysis. $P<0.05$ was considered statistically significant, *ASA* American Society of Anesthesiologists, *CT* computed tomography, *OR* odds ratio, *CI* confidence interval

patient factors could result in necrotic collections becoming walled-off early or late. More research on this topic is, however, needed.

Our study has several limitations. First, for this study, CTs were assessed by one abdominal radiologist. Therefore, no interobserver agreement could be calculated. Since other studies show good agreement for the type of necrotic collection, presence of intraluminal gas in necrotic collections, and presence of a wall among experienced radiologists,[18] we expect our results to be reproducible. Second, full blinding of CTs was unfortunately not feasible. The radiologist was aware of the date and the presence of prior CTs, but was blinded to date of symptom onset and the clinical course. Third, follow-up CTs were not routinely (for example, weekly) performed but rather on the discretion of treating physicians, often based on the change in a patient's condition. This is in line with standard practice as routinely performing CT is not justifiable out of costs and radiation burden perspectives. Fourth, CTs were executed with varying CT protocols. All CTs, however, were performed with a multislice technique with 3-mm reconstructions and were contrast-enhanced in the pancreatic and/or portal venous phase. Also, in most cases, reformatted images were available for review. Therefore, we feel that the finding of gas within collections was easily visible whenever present. Fifth, we defined "clinically (relevant) walled-off necrosis" as necrotic collections that are largely or fully encapsulated. We feel that in clinical practice, the distinction between collections that are not or only moderately encapsulated is treated differently (non-invasive therapy) compared with those that are largely or fully encapsulated (invasive therapy possible). More data are needed to determine whether this definition more closely relates to clinical management than the original definition.

Results of this study could have therapeutic implications because the knowledge of gas configurations and early encapsulation might influence the timing to proceed to an earlier invasive intervention in a subset of patients with infected necrosis. Current international guidelines, however, advise to postpone invasive intervention for at least 4 weeks in patients with (suspected) infected necrotizing pancreatitis until walled-off necrosis is present because intervention is believed to be safer in walled-off necrosis (e.g., less bleeding).[5,6] This advice is primarily based on studies in which patients underwent early primary open necrosectomy (within first 2 weeks) which was associated with worse outcome.[19–21] Nowadays, standard treatment of infected necrosis is primary catheter drainage. At least 35–50% of patients do not need additional necrosectomy after catheter drainage and this is associated with a lower risk for complications.[7,22] Since catheter drainage is the first step of treatment which does not require fully encapsulated necrotic collections, some suggest that early and proactive drainage could prevent clinical deterioration, improve outcome, and shorten hospital stay.[23,24] This hypothesis is currently being studied in the Dutch multicenter randomized controlled POINTER trial (ISRCTN33682933). This study compares immediate catheter drainage with postponed catheter drainage in patients with proven or suspected infected necrotizing pancreatitis.

In conclusion, opposed to common views, gas configurations and walled-off necrosis are seen in every phase of the disease in patients with necrotizing pancreatitis. This may have therapeutic implications in a subset of patients with infected necrosis and early walled-off necrosis.

Authors' Contributions TLB designed the study protocol and evaluated the CTs. MGB and HCvS collected the clinical data. JvG, SvB, and MCvB collected and analyzed the data. JvG drafted and revised the manuscript. SvB, MCvB, MGB, PF, HvG, HCvS, and TLB critically edited the manuscript and approved the final version.

Funding Information Parts of this research were funded by Fonds NutsOhra, the Netherlands, grant number 1404-044.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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