Running Head: Stone removal after obstructive pyelonephritis

Postoperative Progress after Stone Removal Following Treatment for Obstructive Acute Pyelonephritis Associated with Urinary Tract Calculi: A Retrospective Study

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Abstract

Purpose: We aim to identify the prevalence and risk factors of three outcomes after stone removal following treatment for obstructive acute pyelonephritis (APN) associated with urinary tract calculi: immediate postoperative febrile urinary tract infection (UTI), stone recurrence, and APN recurrence during the follow-up period.

Materials and Methods: We retrospectively review the charts of 107 patients who underwent stone removal following treatment for obstructive APN associated with urinary tract calculi. Logistic regression analysis is used to identify the factors that contribute to postoperative febrile UTI after stone removal. Cox proportional hazard analyses are used to identify the factors contributing to stone recurrence and APN recurrence during the follow-up period.

Results: Postoperative febrile UTI was observed in 23 out of the 107 patients (21.5%). Multivariate logistic regression analysis revealed that female sex ($P = .02$) and having multiple stones ($P < 0.01$) were independently significant predictors of postoperative febrile UTI. One-year recurrence-free survival rates of stone disease and APN were 76.1% and 82.5%, respectively. Multivariable cox proportional hazard analyses revealed that residual fragments were the only significant risk factor for stone recurrence ($P < 0.01$) and marginally

significant for APN recurrence (P = .05).

Conclusion: Patients presenting obstructive APN can develop postoperative febrile UTI after active stone removal with high frequency and the risk factors are female sex and having multiple stones. Residual fragments after stone removal in patients with obstructive APN can cause stone and APN recurrence, indicating that complete removal of stone fragments ≥ 4 mm is imperative to the management of the disease.

Introduction

Obstructive acute pyelonephritis (APN) associated with upper urinary tract calculi is one of the main emergency diseases in the urological field. It may progress to severe sepsis and become life-threatening. Despite intensive care and emergency urinary drainage, the mortality rate is reported to be around 2% [(1)]. Several studies of the predictors of progression of sepsis have therefore been reported and clinicians have attempted to effectively treat this disease by risk stratification [(2, 3)].

EAU Guidelines on Interventional Treatment for Urolithiasis (2016) specify that obstruction and infection caused by stones are

indications for active stone removal [4], and stone removal is considered to be necessary for most of these patients. Treatment for patients presenting obstructive APN secondary to upper urinary tract calculi should comprise not only amelioration of the infection, but also stone removal. Stone removal surgery has become effective and safe, but there are sometimes severe postoperative complications [5]. There are concerns about immediate postoperative pyelonephritis, especially when active stone removal is performed for patients after treatment of obstructive APN. In addition, there are also concerns about recurrence of stones and APN recurrence during the follow-up period after active stone removal. However, few studies have reported these problems.

The current study aims to examine postoperative progress after active stone removal and to identify the predictors of three outcomes: immediate postoperative febrile urinary tract infection (UTI), stone recurrence, and APN recurrence during the follow-up period.

Materials and Methods

Patients

Between May 2006 and August 2013, 166 patients were treated for obstructive APN associated with urinary tract calculi at the Wakayama Medical University Hospital, Wakayama Rosai Hospital and Kinan Hospital. Of these patients, five were transferred to other medical

facilities after acute-phase treatment, 34 experienced spontaneous stone expulsion, five underwent nephrectomy and 15 underwent conservative treatment without active stone removal. Enrolled in this study, therefore, were the 107 patients who underwent stone removal following treatment for APN (**Figure 1**). In accordance with our treatment policy, patients continued to have antibiotic treatment by cephem-based antibiotics or carbapenem-based antibiotics for at least two weeks and they underwent active stone removal after improvement of their infection was confirmed. Placement of drainage tubes was left to the judgment of attending physicians. After stone removal, we performed regular follow-up of patients by using kidney-ureter-bladder (KUB) film and ultrasonography every six months and non-contrast computed tomography (NCCT) every few years.

This study was approved by the institutional review board of Wakayama Medical University (approval number 1953). While written informed consent to participate in this study was not obtained from patients since this study was a retrospective observational study for ordinary medical practice, information about this clinical study was disclosed on institutional web pages and displayed in each hospital's visitor consultation rooms. Patient's data would have been excluded had any patient objected to participation, but no patients did so.

Surgical Techniques

Ureteroscopy (URS)

The procedure was performed with the patient in the dorsal lithotomy position under general anesthesia. In distal ureteral stones cases, 7.5 Fr semi-rigid ureteroscope (Karl Storz, Germany) was used. In the cases with stones in another location, flexible ureteroscope (URF-P5/URF-V, OLYMPUS, Japan) was used for the main procedure. The stones were fragmented using a 200 μm Versa Pulse Ho:YAG laser (Lumenis, Israel). Stone fragments were extracted by stone basket. At the end of each procedure, a double-J ureteric catheter was routinely placed.

Percutaneous nephrolithotomy (PCNL)

The procedure was performed with the patient in the prone split-leg position under general anesthesia. Flexible cystoscopy was performed first to cannulate the ureteral orifice with a 0.035 mm guidewire that was passed into the upper urinary tract under fluoroscopic guidance. Next, a 12/14 Fr Flexor® ureteral access sheath (Cook Medical, USA) was inserted to allow frequent passage of the ureteroscope (URF-P5/URF-V, OLYMPUS, Japan) to the site of the calculi. Calyceal puncture was performed under ultrasonographic and fluoroscopic guidance. Antegrade access was established by one-step dilation and placement of the 16.5/19.5 Fr operating sheath. Lithotripsy was

performed by using a 12 Fr Miniature Nephroscope (Karl Storz, Germany) and LithoClast® (Boston Scientific, USA). Stones were broken into small fragments and washed out through the sheath by retrograde irrigation. At the end of each procedure, a double-J ureteric stent and a 16 Fr nephrostomy tube were routinely placed.

Predictors

Patient demographics (age, sex, performance status and anamnesis regarding previous history of urinary tract calculi) and clinical data (stone location, stone size, number of stones and laboratory data at the consultation) were collected retrospectively. Clinical records were also reviewed and information about urinary drainage, methods of stone removal, and residual stones after stone removal was collected.

Patients who had diabetes mellitus or were being administered anti-cancer agents or immunosuppressive agents were included in the compromised hosts group. Stone size was defined as the maximum diameter in millimeters and determined by KUB film or NCCT. The presence of residual stones was determined using KUB film or NCCT within three months of stone removal and residual stones were defined as residual fragments ≥ 4 mm.

Outcomes and Statistical Analyses

We investigated immediate postoperative febrile UTI after stone removal, stone recurrence and APN recurrence during the follow-up period, and analyzed the factors contributing to these three outcomes. Postoperative febrile UTI was defined as body temperature > 38°C which required additional antibiotic treatment. Stone recurrence was defined as the appearance of symptoms caused by urinary tract calculi, intervention for urinary tract calculi, and the appearance or growth of stones on imaging tests. Logistic regression analysis was performed to identify the factors contributing to immediate postoperative febrile UTI after stone removal. Univariate and multivariate analyses were performed to identify the factors contributing to stone recurrence and APN recurrence during the follow-up period in cox proportional hazard model. For all statistical tests, $P < 0.05$ was considered significant. Recurrence rates of stone disease and APN were calculated by the Kaplan-Meier method. All statistical analyses were performed using JMP Pro 12 (SAS Institute, USA).

Results

Patient demographics and clinical data are shown in **Table 1**. The median age was 69 years (range: 24-94 years) and 72 patients (67.3%) were female. The median stone size was 9.0 mm (range: 3.0-35.0 mm). Seventy patients (65.4%) developed systemic inflammatory response syndrome (SIRS) and 93 patients (86.9%) received urinary drainage by either ureteral stenting (n = 75, 70.1%) and percutaneous

nephrostomy (n = 18, 16.8 %). Of the 107 patients, 52 patients (48.6%) underwent extracorporeal shock wave lithotripsy (ESWL), 49 patients (45.8%) underwent URS and six patients (5.6%) underwent PCNL. Overall, residual stones were observed in 22 patients (20.6%). Ninety patients (84.1%) had regular follow-up after stone removal in the respective institutions.

1) Immediate postoperative febrile urinary tract infection

Postoperative febrile UTI (Clavien-Dindo classification grade 2) was observed in 23 out of the 107 patients (21.5%). **Table 2** shows the results of univariate and multivariate logistic regression analyses of factors which predict postoperative febrile UTI. Among the potential variables, female sex (P = .01), ureteral stones (P = .02), multiple stones (P < 0.01) and endoscopic therapies (P = .04) were statistically significant predictors of febrile UTI based on univariate analysis. From multivariate analysis, female sex (P = .02) and multiple stones (P < 0.01) were independently significant predictors of postoperative febrile UTI.

2) Stone recurrence during the follow-up period

Stone recurrence was observed in 22 out of the 90 patients who had regular follow-up (mean follow-up period: 17.7 months) and the one-year stone recurrence-free survival rate was 76.1%. **Table 3** shows the results of univariate and multivariate cox proportional hazard

analyses of factors which predict stone recurrence during the follow-up period. Among the potential variables, statistically significant predictors of stone recurrence during the follow-up period of univariate analysis were younger age (P = .02), multiple stones (P < 0.01) and residual fragments (P < 0.01). One-year stone recurrence-free survival rates in patients with or without residual fragments were 39.7% and 86.1%, respectively (P < 0.01, **Figure 2A**). In multivariate analysis, residual fragments were the only independent significant predictor of stone recurrence (P < 0.01).

3) APN recurrence during follow-up period

APN recurrence was observed in 20 out of the 90 patients who were followed (mean follow-up period: 17.5 months) and the one-year APN recurrence-free survival rate was 82.5%. **Table 4** shows the results of univariate and multivariate cox proportional hazard analyses of factors which predict APN recurrence during the follow-up period. Among the potential variables, statistically significant predictors of APN recurrence were younger age (P < 0.01), poor performance status (P = .03), multiple stones (P = .04) and residual fragments (P < 0.01) during the follow-up period of univariate analysis. One-year APN recurrence-free survival rates in patients with or without residual fragments were 48.5% and 92.6%, respectively (P < 0.01, **Figure 2B**). In multivariate analysis, residual fragments were not significant,

but were considered a possible predictor of APN recurrence (P = .05).

Discussion

We examined the postoperative progress after active stone removal in patients presenting obstructive APN secondary to upper urinary tract calculi, and identified the predictors of immediate postoperative febrile UTI, stone recurrence and APN recurrence during the follow-up period. In this study, we made two important clinical observations.

First, patients presenting obstructive APN can develop postoperative febrile UTI after active stone removal with high frequency. Risk factors are female sex and presence of multiple stones.

Most of the patients in the present study underwent URS or ESWL. Previous studies reported that the rate of postoperative fever or sepsis after treatment was between 1.1 and 12.6% [6-8]. On the other hand, Lingeman et al. (1986) reported that 15.5% of their 1,416 patients undergoing ESWL treatment developed febrile UTI [9]. The incidence of postoperative febrile UTI in our study was 21.5%, which was much higher than those in previous studies. This might suggest that a history of obstructive pyelonephritis is the main risk factor for postoperative febrile UTI.

In previous studies, presence of multiple stones has been reported to be a predictor of infectious complications in URS cases [10,11]. This factor was significantly associated with postoperative febrile UTI in our patients also. Therefore, stone removal for patients with obstructive pyelonephritis caused by multiple stones requires caution. Although few studies have reported that the incidences of postoperative febrile UTI are different depending on sex, female sex was a risk factor in our study. This might be because the proportion of magnesium ammonium phosphate stones in females is generally higher than in males. However, much of the data about stone composition was unavailable in the current study.

Furthermore, the presence of residual fragments after stone removal in patients with obstructive APN can cause APN recurrence and stone recurrence with high frequency. Several studies on the natural history of residual stones after URS, ESWL and PCNL have been reported. Chew et al. (2016) and Atis et al. (2011) examined the natural history of fragments after ureteroscopy and reported that fragments > 4 mm were associated with more complications [12,13]. Rebuck et al. (2011) reported that 19.6% of patients experienced stone-related events even if their residual fragments were ≤ 4 mm [14]. In ESWL treatment, residual fragments of > 5 mm have generally been considered a failure of ESWL. Buchholz et al. (1997) examined the natural history of residual fragments < 5 mm after ESWL and did not recommend

more invasive attempts to clear all minor fragments because all of the residual fragments were asymptomatic and only 2% showed stone regrowth [15]. On the other hand, in recent studies, close follow-up or positive therapeutic intervention has been recommended, even if residual fragments after ESWL are ≤ 5 mm, because they can become symptomatic [16-18]. As for the natural history of residual stones after PCNL, Raman et al. (2009) analyzed 527 patients who underwent PCNL and reported that 42 patients (8%) had residual fragments and that 18 of these 42 patients (43%) experienced a stone-related event [19]. In their study, maximum residual fragment size > 2 mm and location in the renal pelvis or ureter were independent significant predictors of stone events.

No studies have reported on the natural history of residual stones after stone removal following the treatment for obstructive APN, to the best of our knowledge. The results of the present study show that residual stones ≥ 4 mm after stone removal following treatment for obstructive APN are an independent significant risk factor for stone recurrence and marginally significant for pyelonephritis recurrence during the follow-up period. Notably, residual fragments can cause acute pyelonephritis recurrence as well as stone recurrence in patients with obstructive acute pyelonephritis with urinary tract calculi. As shown in **Figure 2**, more than half of the patients with residual fragments experienced stone recurrence or pyelonephritis recurrence within one year. Even when compared with the previous studies

described above, these recurrence rates seem to be higher. Complete removal of stone fragments ≥ 4 mm is therefore essential for patients after obstructive pyelonephritis associated with urinary tract calculi.

There are several limitations to the present study. First, it is a retrospective study with relatively small number of patients undertaken across several centers. Second, the evaluation method of residual fragments differed between the patients (i.e. CT and KUB). Third, the definition of residual stones ≥ 4 mm might be criticized as inappropriate since even residual stones < 4 mm can cause symptomatic stone events and stone recurrence. However, no significant differences were noted in stone recurrence and APN recurrence between patients without any residual stones (completely stone-free) and those with residual stones of 1 mm (HR, 1.82; 95% CI, 0.43-6.99 and HR, 0.28; 95% IC, 0.04-1.41, respectively) or 2-3 mm (HR, 1.11; 95% CI, 0.15-5.41 and HR, 0.54; 95% CI, 0.07-2.71, respectively). It is therefore reasonable to use the definition of residual stones ≥ 4 mm in this study. In addition, several factors that might influence postoperative complications, such as preoperative urine culture, stone composition and operation time, were not included in our analysis because the data were unavailable.

Nonetheless, this study showed that residual fragments after stone removal in patients with obstructive APN can cause APN recurrence

as well as stone recurrence with high frequency. A multicenter prospective analysis is required to overcome these limitations.

Conclusions

Patients presenting obstructive APN can develop postoperative febrile UTI after active stone removal with high frequency. The risk factors are female sex and presence of multiple stones. Residual fragments after stone removal in patients with obstructive APN can cause APN recurrence as well as stone recurrence with high frequency. Stone removal without leaving residual fragments is therefore more important for these patients.

List of Abbreviations

APN: acute pyelonephritis

KUB: kidney-ureter-bladder

NCCT: non-contrast computed tomography

SIRS: systemic inflammatory response syndrome

ESWL: extracorporeal shock wave lithotripsy

URS: ureteroscopy

PCNL: percutaneous nephrolithotomy

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Conflicts of interest

None declared.

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Table 1. Patient demographics and clinical data

No. of patients	107
Age, years	69 (24-94)
Gender, n (%)	
Male	35 (32.7)
Female	72 (67.3)
Compromised host, n (%)	24 (22.4)
Karnofsky Performance Scale≤70%, n (%)	34 (31.8)
Previous history of urinary tract calculi, n (%)	38 (35.5)
Stone	
Side, n (%)	
Right	52 (48.6)
Left	55 (51.4)
Location, n (%)	

renal calyx	3 (2.8)
ureteropelvic junction	17 (15.9)
upper ureter	54 (50.5)
middle ureter	24 (22.4)
lower ureter	9 (8.4)
Size, mm	9.0 (3.0-35.0)
multiple stones, n (%)	40 (37.4)
Laboratory data at the consultation	
WBC count (/μL)	12400 (1900-37200)
CRP (mg/dL)	12.19 (0.07-42.14)
SIRS, n (%)	70 (65.4)
Drainage, n (%)	93 (86.9)
Ureteral stent	75 (70.1)
Percutaneous nephrostomy	18 (16.8)

Abbreviations: WBC: white blood cell, CRP: C-reactive protein, SIRS: systemic inflammatory response syndrome

Continuous variables are shown in "median (range)" form.

Table 2. Logistic regression analyses of associations between various parameters and postoperative febrile UTI after stone removal (N=107)

Variable				Univariate analysis			Multivariate analysis		
		N	Number of UTI	OR	95% CI	P value	OR	95% CI	P value
Age, years				0/99	0.96 - 1.03	.64			
Gender	Female	72	20	4/10	1.28 - 18.39	.01	5/02	1.21 - 20.66	.02
	Male	35	3						
Compromised host	+	24	7	1/72	0.59 - 4.76	.31			
	-	83	16						
Karnofsky Performance Scale	≤ 70%	34	5	0/53	0.16 - 1.48	.23			
	≥ 80%	73	18						
Stone location	Ureteral stone	87	22	6/43	1.22 - 118.81	.02	6/27	0.70 - 55.57	.09
	Renal stone	20	1						
Stone size, mm				1/03	0.96 - 1.10	.43			

Stone number	Multiple	40	17	7/51	2.76 - 23.05	< 0.01	9/71	3.01 - 31.29	< 0.01
	Single	67	6						
CRP, mg/dL				0/98	0.93 - 1.03	.37			
SIRS	+	70	6	1/65	0.62 - 4.99	.32			
	-	37	17						
Drainage	+	93	19	0/64	0.19 - 2.54	.50			
	-	14	4						
Method of stone removal	URS/PCNL	55	16	2/64	1.01 - 7.48	.04	3/03	0.93 - 9.82	.06
	ESWL	52	7						

Abbreviations: CRP: C-reactive protein, SIRS: systemic inflammatory response syndrome, URS: ureteroscopy, PCNL: percutaneous nephrolithotomy, ESWL: extracorporeal shock wave lithotripsy

Table 3. Cox proportional hazard analyses of associations between various parameters and stone recurrence during follow-up period (N=90)

Variable				Univariate analysis			Multivariate analysis		
		N	Number of Events	HR	95% CI	P value	HR	95% CI	P value
Age, years				0/96	0.93 - 0.99	.02	0/98	0.95 - 1.01	.30
Gender	Male	30	5	0/50	0.17 - 1.28	.15			
	Female	60	17						
Karnofsky Performance Scale	≤ 70%	20	7	1/53	0.59 - 3.65	.36			
	≥ 80%	70	15						
Compromised host	+	17	5	1/76	0.58 - 4.48	.26			
	-	73	17						
Stone history	Recurrent stone former	34	11	1/05	0.43 - 2.52	.90			
	Non-recurrent stone former	56	11						
Stone number	Multiple	34	15	3/26	1.36 - 8.60	< 0.01	2/13	0.78 - 5.82	0.13
	Single	56	7						
Method of stone removal	URS/PCNL	44	11	0/97	0.41 - 2.26	.93			
	ESWL	46	11						
Residual fragments	+	18	10	5/18	2.12 - 12.64	< 0.01	3/72	1.44 - 9.57	< 0.01

	-	72	12

Abbreviations: URS: ureteroscopy, PCNL: percutaneous nephrolithotripsy, ESWL: extracorporeal shock wave lithotripsy

Table 4. Cox proportional hazard analyses of associations between various parameters and recurrence of APN during follow-up period (N=90)

Variable				Univariate analysis			Multivariate analysis		
		N	Number of Events	HR	95% CI	P value	HR	95% CI	P value
Age, years				0/96	0.93 - 0.99	< 0.01	0/97	0.94 - 1.00	.14
Gender	Male	30	8	1/42	0.55 - 3.44	.45			
	Female	60	12						
Karnofsky Performance Scale	≤ 70%	20	9	2/70	1.09 - 6.55	.03	2/26	0.91 - 5.60	.07
	≥ 80%	70	11						
Compromised host	+	17	5	1/89	0.61 - 4.92	.24			
	-	73	15						
Stone history	Recurrent stone former	34	10	1/15	0.46 - 2.86	.75			
	Non-recurrent stone former	56	10						
Stone number	Multiple	34	12	2/48	1.01 - 6.43	.04	1/20	0.39 - 3.61	.74
	Single	56	8						
Method of stone removal	URS/PCNL	44	8	1/03	0.67 - 1.58	.89			

	ESWL	46	12						
Residual fragments	+	18	9	3/67	1.46 - 9.11	< 0.01	2/65	0.96 - 7.25	.05
	-	72	11						

Abbreviations: URS: ureteroscopy, PCNL: percutaneous nephrolithotripsy, ESWL: extracorporeal shock wave lithotripsy

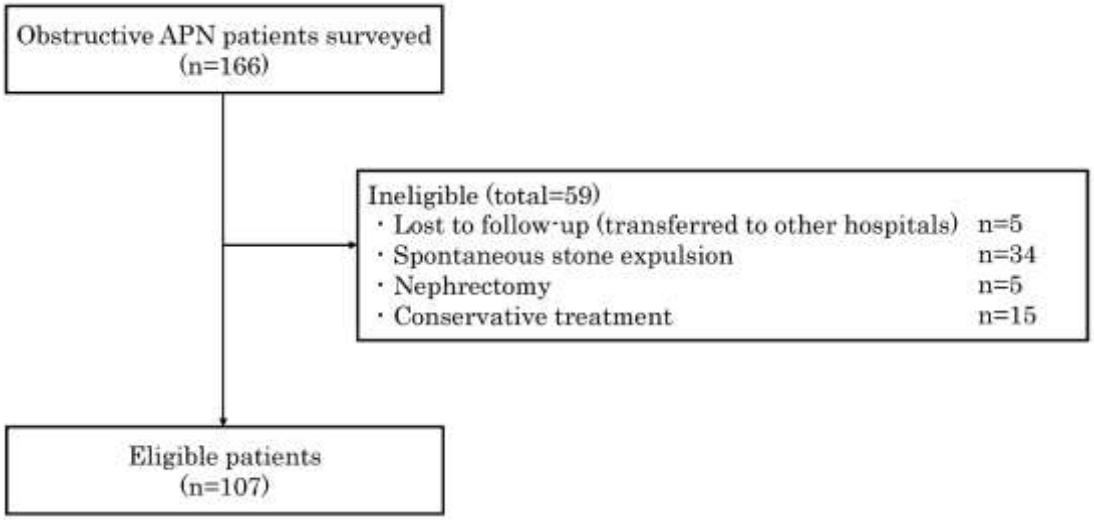
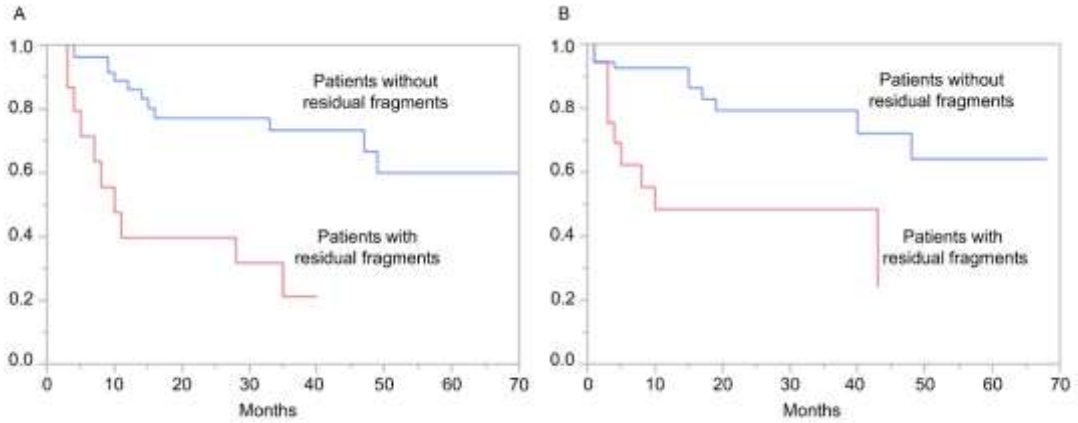


Figure 1. Study cohort flow diagram. APN: acute pyelonephritis.



]Figure 2. Comparison of (A) stone recurrence-free survival rate and (B) pyelonephritis recurrence-free survival rate between patients with residual fragments and patients without.