The effect of respiratory-gated positron emission tomography/computed tomography in patients with pancreatic cancer

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Abstract

Our aim of this study was to evaluate prospectively in patients with pancreatic cancer the effects of respiratory-gating during PET/CT acquisition on the determination of lesion volume and to measure tracer uptake. *Our research* included 36 patients diagnosed with pancreatic cancer. They underwent conventional whole-body PET/CT and subsequently respiratory-gated PET/CT of the upper abdomen. Based on list-mode PET acquisition data, respiratory-gated and non-gated images were created. Maximum standardized uptake values (SUV_{max}) and lesion volumes were compared between gated and non-gated images and also the rate of increase in SUV_{max} based on lesion size. *Results showed that* respiratory gating was successful in 34/36 patients. The median non-gated SUV_{max} was 6.2±2.1 and was 8.1±2.5 for respiratory-gated ($P<0.01$). Lesion volumes could be calculated in 27/34 patients. The median non-gated lesion volume was 5.82±5.57cm3 and 4.31±4.56cm^3 for respiratory-gated ($P<0.01$). Furthermore, small lesions of ≤2cm had a significantly higher proportion of increased SUV_{max} compared to large lesions of >2cm ($P=0.016$). *In conclusion,* respiratory-gated PET/CT for patients with pancreatic cancer reduced respiratory motion artifacts and allowed significantly higher SUV_{max} to be obtained. In addition, the rate of increase in SUV_{max} tended to be higher in patients with pancreatic cancers of less or equal to 2cm diameter.

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Introduction

Positron emission tomography (PET) detects gamma rays originating from a radiotracer such as fluorine-18-fluorodeoxyglucose (^{18}F-FDG), a glucose analog used for imaging. In addition, enables functional testing to determine glucose metabolic increases in tumor cells. Positron emission tomography/computed tomography (PET/CT), a hybrid of PET and CT, was developed in 2000. Because this technique improved diagnostic accuracy, the demand for PET/CT quickly spread. Currently, is widely used for cancer diagnosis staging, evaluation of treatment, and diagnosis of recurrent cancer disease [1-10].

A major issue using PET/CT is respiratory motion artifacts. A whole-body PET scan normally takes 10-20min and is performed while the patient breathes normally at rest. Respiratory motion causes blurring of a lesion, which may result in overestimating lesion size and underestimating the SUV of the lesion. On the other hand, CT imaging can be completed during a pause in the breathing cycle. The difference in imaging conditions between these two techniques causes an inaccurate attenuation correction and image fusion, which in turn may cause the SUV to be further underestimated and may result in the spatial uncoupling of metabolic and structural imaging [11, 12]. In order to overcome this problem, a respiratory-gated technique was developed, which synchronizes PET and CT acquisition to the respiratory motion using a respiratory-motion tracking system [11, 13]. A large number of studies have shown that this method improves the estimates of lesion size and the accuracy of SUV, particularly in the lung regions [14-16]. However, this technique is not yet routinely used in clinical practice of PET imaging [11].

It is assumed that organs in the epigastric region that are proximal to the diaphragm, including the pancreas, are also susceptible to respiratory motion. However, very few studies have investigated the effect of respiratory-gating in pancreatic disease. Kasuya et al. (2013) reported role of respiratory gated PET/CT for pancreatic tumor(s), but didn't compare gated image to non-gated at the same time [17]. Thus, in this study, we investigated the utility of respiratory-gated PET/CT in patients with pancreatic cancer.

Subjects and methods

We studied 36 patients with histologically or cytologically confirmed pancreatic cancer at the Department of Gastroenterology and Metabolism, Hiroshima University Hospital and related facilities between September 2010 and December 2012. This study was approved by the Institutional Review Board of our Institution, and we obtained informed consent from all patients. A PET/CT scan was performed using a Discovery ST Elite Performance scanner (General Electric Medical Systems, Milwaukee, WI, USA). The respiratory motion monitor used in this study was a Real-time Position Management respiratory-gating system (RPM, Varian Medical Systems, Palo Alto, CA, USA), which provides synchronization between the patient's respiratory cycle and data acquisition (Fig. 1).

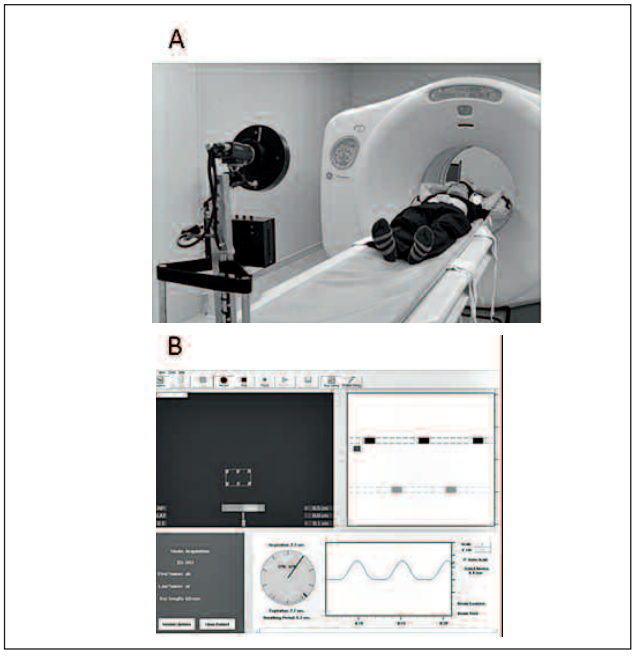

Figure 1. Respiratory motion tracking system. (A) RPM uses an infrared camera that is mounted on the PET/CT table and an infrared-reflective marker block that is fixed to each patient's upper abdomen so it is visible to the camera at all times and guarantees continuous respiratory motion tracking. (B) The motion of the block is displayed by a graphic interface on the RPM workstation.

We initially explained the respiratory-gating method to patients; it was later determined whether they could maintain constant respiration during the RPM monitoring. To obtain a serum glucose level of less than 150mg/dL, patients fasted for at least 4h before administration of 3.7MBq/kg of ^{18}F-FDG, and 60min later, a conventional whole-body PET/CT image was acquired (CT parameters: 120kV, 120mA and thickness of 5mm). Subsequently, respiratory-gated PET/CT of the epigastric region was performed after 80min, primarily focusing on the pancreas. Respiratory-gated CT data were acquired in cine mode with the following parameters: 10mA, 120kV and slice thickness of 2.5mm. It was performed in the range of the upper abdomen while monitoring the respiratory motion by RPM. Gated PET data were also acquired in one bed (15.7cm), primarily of the pancreas for 15min while monitoring breathing by RPM. The respiratory cycle was divided into 5 phases, and divided PET data were reconstructed using 3-D ordered subset expectation maximization algorithm with 2 iterations and 15 subsets, followed by 5.14mm full width at half maximum (FWHM). The matrix sizes were 128×128 for PET images and 512×512 for CT images. Attenuation correction and image fusion were performed for each one phase of PET data by using the same phase of cine CT data (Fig. 2). SUV_{max} was defined as the high-

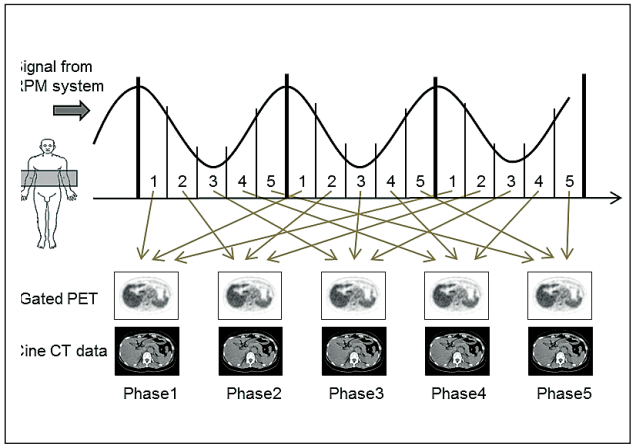

Figure 2. Data acquisition and processing in gated PET/CT. PET data were acquired in list-mode while monitoring breathing by RPM. The respiratory cycle was divided into 5 phases. Attenuation correction and image fusion were performed on each phase of cine CT data.

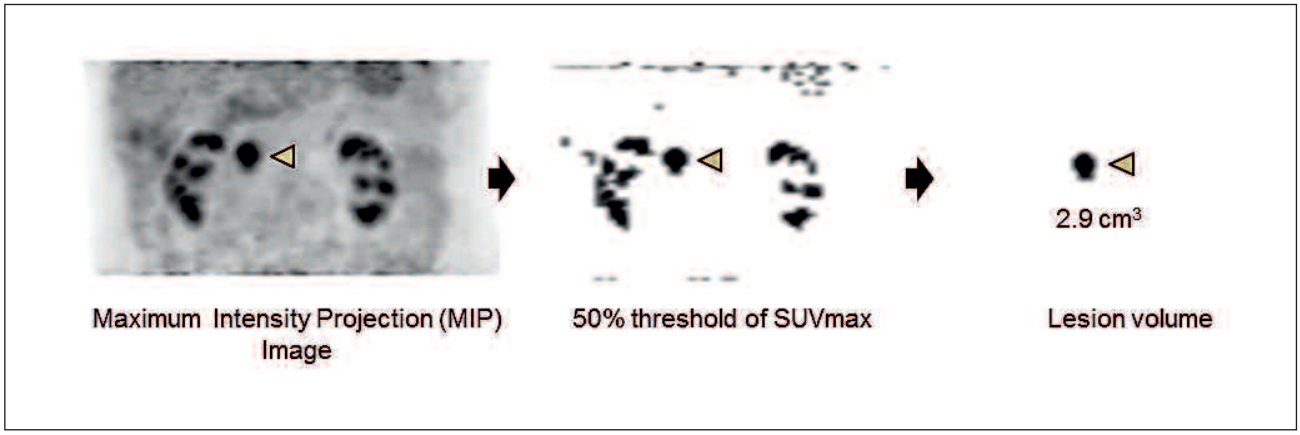

Figure 3. Calculation method of lesion volume. Arrowhead; a lesion in the pancreas.

est pixel value related to the neoplasm and was computed using the following formula: SUV_{max}=maximum activity concentration in the neoplasm (kBq/mL)/[injected dose (MBq)/body weight (kg)]. For gated PET/CT, SUV_{max} was calculated for each phase. We selected the highest uptake phase ("Best-phase") as the respiratory-gated SUV_{max}. Non-gated images were created from the pre-divided list-mode acquisition data, and the non-gated SUV_{max} was calculated for the same period. Lesion volume was defined as 50% of the threshold volume for SUV_{max} (Fig. 3), and gated and non-gated values for each volume were measured. Then, we compared SUV_{max} and the lesion volume between gated and non-gated images. In addition, the rate of increase in SUV_{max} was calculated and compared between small lesions of less or equal to 2cm and large lesions of more than 2cm in diameter.

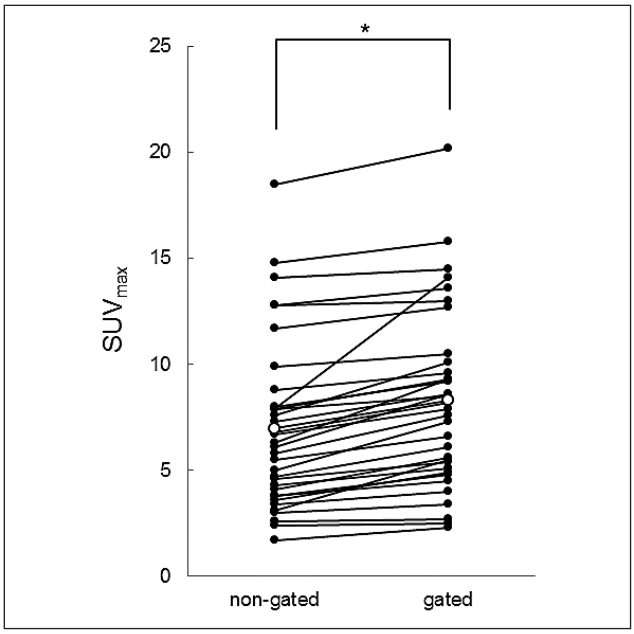

Figure 4. Comparison of SUV_{max} in non-gated and gated PET/CT studies. Gated SUV_{max} was significantly higher than non-gated SUV_{max} (*P<0.01).

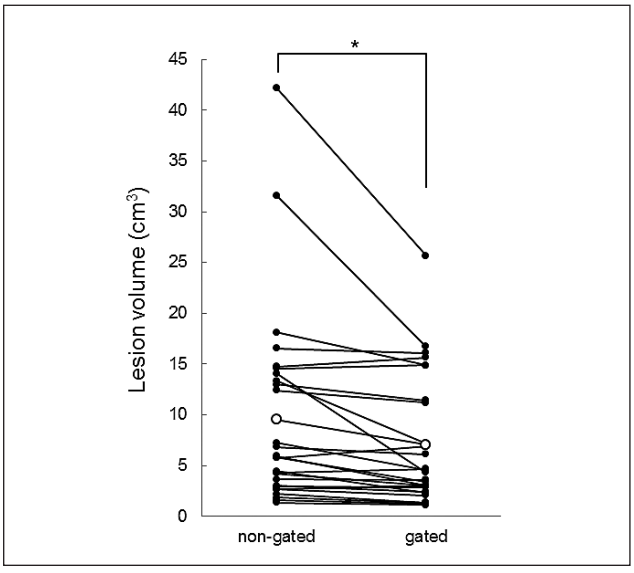

Figure 5. Comparison of lesion volume (cm^3) in non-gated and gated PET/CT studies. The respiratory-gated lesion volume was significantly smaller than the non-gated volume (*P<0.01).

Data analysis

All results are shown as median±quartile deviation. Wilcoxon t-test and Mann-Whitney U-test were used for statistical comparisons. P values of <0.05 were considered statistically significant.

Results

Of the 36 patients, 34 were able to maintain regular respiration. The characteristics of these 34 patients are shown in Table 1. All patients showed increased uptake of ^{18}F-FDG in the primary lesion. Besides the primary lesion, ^{18}F-FDG uptake was found in peripancreatic lymph nodes (n=4), paraaortic lymph nodes (n=2), liver metastases (n=4), and in the thoracic vertebrae (n=1). The median non-gated SUV_{max} was 6.2±2.1. The median gated SUV_{max} was significantly increased to 8.1±2.5 (P<0.01; Fig. 4). Lesion volumes could be measured in 27/34 patients. The median respiratory non-gated volume was 5.82±5.57cm^3 and the median respiratory-gated volume was 4.31±4.56cm^3. The respiratory-gated

***Table 1**. Characteristics of the 34 patients of this study*

Sex (men/women)	19/15
Age (y)	56-89 (mean±SD; 71.4±9.14)
Tumor size (mm)	10-72 (mean±SD; 29.3±13.0)
BMI (kg/m²)	15.4-27.2 (mean±SD; 21.9±3.26)
Location (head/body or tail)	26/8

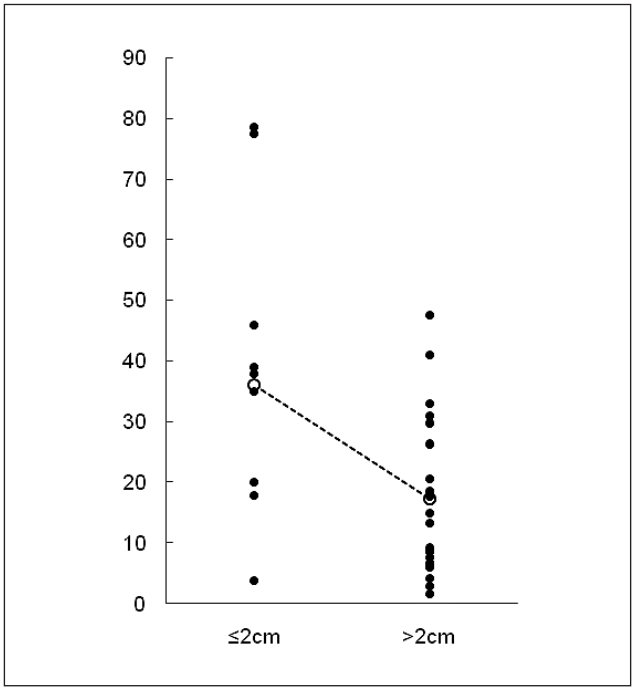

Figure 6. Comparison of SUV_{max} increase rate in tumor size (≤2cm vs. >2cm). Small lesions of ≤2cm showed a significantly greater rate of increase than large lesions of >2cm (*P=0.016).

lesion volume was significantly smaller than the non-gated volume (P<0.01; Fig. 5). Small lesions of ≤2cm were found in 9 patients, and large lesions of >2cm were found in 25 patients. The median rate of increase in SUV_{max} for small lesions was 36.0%±21.4%, whereas the median rate of increase in SUV_{max} for large lesions was 17.4%±8.13%. Small lesions of ≤2cm exhibited a significantly greater rate of increase in SUVmax than large lesions of >2cm (P=0.016; Fig. 6).

Discussion

Pancreatic cancer has few characteristic clinical symptoms in the early stage; therefore, diagnosing this disease is extremely difficult and the prognosis is very poor [18]. Normally, ultrasound and multiphase contrast-enhanced CT are performed for parenchymal analysis and visualization of surrounding vessels. Combined with magnetic resonance cholangiopancreatography, endoscopic ultrasound, endoscopic retrograde cholangiopancreatography, PET, or other imaging modalities, diagnosis was made after considering all data and was confirmed by histopathology. Imaging by PET enables functional testing and can measure tumor activity, so it is one of the more important diagnostic tests for pancreatic cancer. A meta-analysis showed that combining PET and CT with the use of iv contrast improved the diagnostic rate of pancreatic cancer [19]. However, the diagnostic rate for PET of small lesion pancreatic cancer is not high. The primary reason for the low rate is the occurrence of the partial volume effect caused by the low spatial resolution of PET [20]. In addition, in organs that are proximal to the diaphragm, respiratory motion artifact is also a source of reduced sensitivity due to blurring of the lesions.

Table 2. *Lesion volume (cm^3) in gated (phase 1-5) and non-gated PET/CT*

No	Gated volume of each phase					Non-gated
	Phase 1	Phase 2	Phase 3	Phase 4	Phase 5	
1	10.85	**7.19**	7.33	9.20	8.69	13.36
2	**14.95**	16.10	16.10	17.96	16.89	16.53
3	8.34	5.89	**4.31**	7.41	12.72	14.08
4	2.51	2.52	**1.94**	2.80	2.08	2.73
5	28.02	27.02	22.20	**16.74**	25.58	31.61
6	**10.06**	12.93	11.42	12.65	11.42	13.01
7	3.09	3.16	2.95	**2.87**	3.45	2.95
8	4.24	5.68	5.60	3.95	**3.59**	3.66
9	14.87	16.02	15.38	17.53	15.52	**14.58**
10	2.30	**1.37**	2.16	2.52	1.65	2.23
11	1.29	1.29	**1.15**	1.37	1.58	1.37
12	6.90	5.01	**3.02**	4.17	4.96	5.96
13	7.19	6.68	6.90	6.90	6.97	**5.75**
14	14.87	**11.21**	13.58	12.29	14.51	12.43
15	7.47	**6.11**	6.54	9.13	7.90	6.83
16	3.95	**3.02**	3.52	3.16	4.46	4.24
17	2.80	**2.25**	2.30	2.26	2.73	4.46
18	18.47	19.04	19.55	17.32	**14.87**	18.11
19	7.83	4.67	9.56	8.48	7.65	**4.31**
20	5.10	4.60	5.75	**4.02**	4.53	7.26
21	**1.37**	**1.37**	1.44	1.44	1.51	1.87
22	3.09	4.17	3.09	3.09	3.16	**2.66**
23	2.52	2.87	2.66	**2.44**	2.66	3.02
24	31.11	**25.65**	37.79	36.86	43.90	42.18
25	5.46	4.38	3.95	5.03	**3.45**	5.82
26	15.30	14.95	15.09	15.16	15.66	**14.73**
27	1.44	1.51	1.44	1.58	**1.29**	1.58

The highest SUV_{max} phase (Best-phase). The smallest volume is written in bold face. The lesion volume of Best-phase was the smallest in 17/27 patients (if the second smallest volume was included, then this number was 24/27 patients).

Diagnosis by PET/CT is primarily affected in the following 3 ways by respiratory motion: a) blurring of the lesion in the PET image; b) fusion discrepancies; and c) inaccurate attenuation correction caused by differences in measurement time. To control the image deterioration due to respiratory motion, particularly in the lung region, a variety of technologies, including breath-holding and respiratory gating, are used [21-23]. In addition, technologies other than RPM, such as pressure and temperature sensors and spirometers, are used in the clinical setting as respiratory-motion tracking systems [24-27].

In this study, performing respiratory-gated PET/CT for patients with pancreatic cancer resulted in increased SUV, decreased accumulated volumes, and improved visibility of lesions, similar to that seen with lung lesions. Thus, the pancreas is an organ that is particularly susceptible to respiratory motion, and a respiratory gating technique should be quite useful. Based on these findings, it is possible that respiratory-gated PET/CT not only improves the ability to diagnose pancreatic cancer but may also be used to accurately set the radiation exposure range when performing radiation therapy.

In this study, a respiratory cycle was divided into 5 phases, with the highest SUV_{max} ("Best-phase") designated as the respiratory-gating value. When considering lesion volumes, the lesion volume of Best-phase was the smallest in most of our patients, particularly in 17/27 patients. If the second smallest volume was included, then this value was increased to 24/27 patients (Table 2). This result indicated that respiratory gating was generally able to minimize motion artifacts in Best-phase. Some of other studies have also adopted Best-phase as respiratory gating value [16, 28], while Kasuya et al (2013) designated SUV_{max} in 3/5 bin (phase 3) as respiratory-gating value based on phantom study [17]. Further consideration about the appropriate phase of respiratory-gating will be needed.

We also investigated lesion size, which showed that pancreatic cancers of ≤2cm had a significantly higher proportion of increased SUVmax compared to cancers of >2cm. Previous studies using respiratory gating to investigate lesion size in the lung region have reported that small lesions have a higher proportion of increased SUV as compared to large lesions [28]. The reason may be that small lesions whose diameters are less than the shift range of respiratory motion are more susceptible to respiratory motions, and thus, respiratory-gating techniques are more effective in small le-

sions compared to large lesions. In the future, using respiratory-gating techniques, it may be possible to detect small pancreatic cancers, which have low detection rates on conventional PET/CT.

There were some limitations in our study. First, the sizes of small lesions in this study were 1-2cm; therefore, the effect of respiratory gating on lesions of <1cm remains unknown. Second, we didn't investigate the finding of malignancy versus benign tumor in this study. Several studies have reported about distinguishing malignancy from benign lesion of pancreas using conventional (non-gated) PET/CT [29-32]. However, the effect of respiratory-gating on differential diagnosis of pancreatic mass has not been clarified. Even in patients with benign diseases, respiratory gating would probably reduce lesion discrepancies and increase SUV. Thus, it will be necessary to compare data acquired with respiratory gating to data acquired with non-gated cases in order to create an independent cut-off value for the SUV of benign tumors. Third, this study included only a small number of cases. Large-scale studies with a large number of cases should be conducted in the future.

In conclusion, in this paper we noticed that respiratory-gated PET/CT in patients with pancreatic cancer reduces image smearing due to respiratory motion and results in significantly decreasing accumulated volume and in increasing SUV_{max} of a pancreatic lesion as compared to conventional PET/CT. In addition, the rate of increase in SUV_{max} tended to be higher in patients with small pancreatic cancers. This method may become a useful tool in detecting small pancreatic lesions and in setting the accurate exposure site for radiation therapy.

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The authors declare that they have no conflicts of interest.

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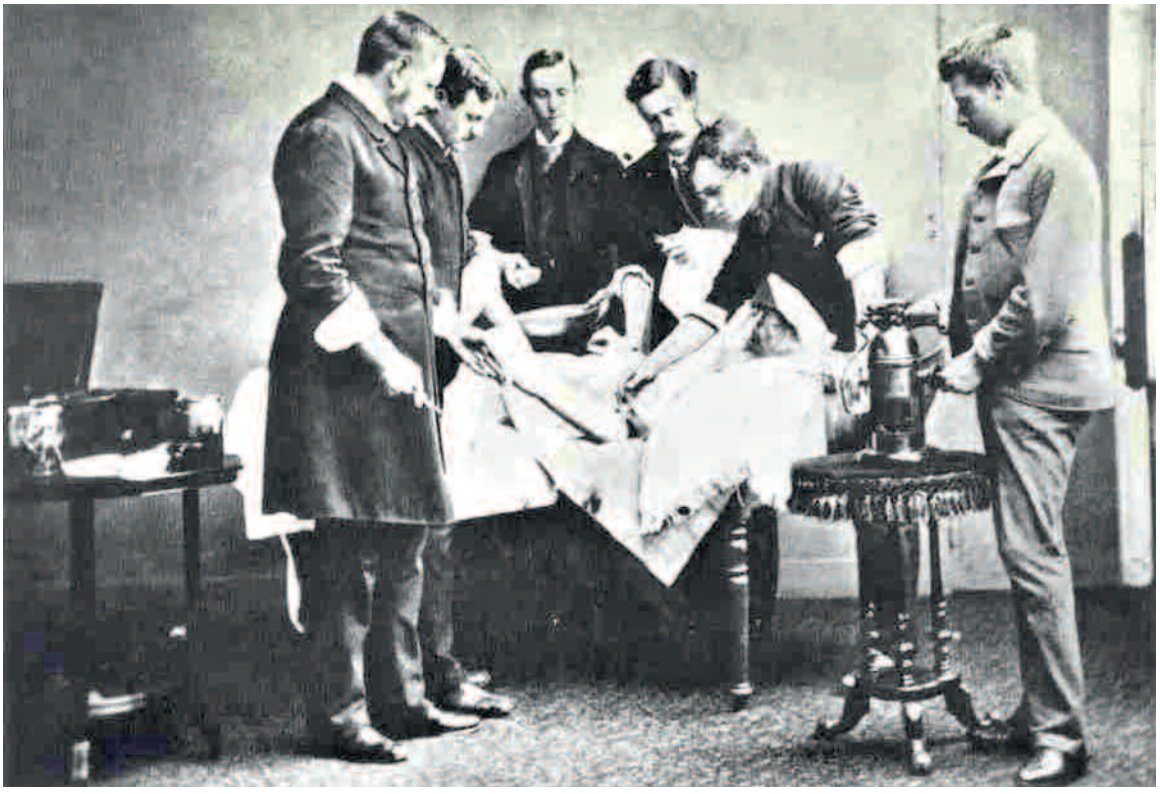

Sir Alexander Ogston performing a surgical operation at the Royal Infirmary of Aberdeen on 1882. Photography