

Lung cancer in situs inversus totalis (SIT) - literature review

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ABSTRACT

We present 21 studies of cases of lung cancer in patients with situs inversus totalis (SIT) published worldwide. The first case was described in 1952. Thirteen patients were from Japan, 4 from Eastern Europe, including 2 Polish cases from the authors' center (Department of Thoracic Surgery, Pomeranian Medical University in Szczecin, Poland), 2 from Western Asia, 1 from the U.S. and 1 from Australia. Male patients (20/21) as well as left-sided lung cancer cases (14/21) and squamous cell carcinoma cases (8/21) dominated in the entire group. Thirteen patients underwent surgical treatment. There were 10 left-sided and 3 right-sided surgical interventions with uneventful intra- and postoperative course. Explorative thoracotomy was performed in one case only on the right side. Upper lobectomy was performed in 5 cases, pneumonectomy in 3 cases, lower bilobectomy and middle lobectomy in one case and lower lobectomy in two cases. Surgery was performed through thoracotomy in 10 cases, VATS-assisted approach in two cases and sternotomy in one case. Descriptions of the surgical anatomy confirmed mirror image of the anatomy in all cases and were consistent with the preoperative CT images. Preoperative diagnosis was discussed including the role of 3-D reconstruction of CT for improving perioperative safety in this group of patients. In conclusion, lung cancer/SIT cases despite inversed but regular anatomy can be operated on radically as cases with normal anatomy with preservation of intraoperative security level.

Key words: lung cancer, situs inversus

INTRODUCTION

Inborn anomalies of organ placement (Situs inversus - SI) can be divided into situs inversus totalis - SIT and incomplete situs inversus. In the second case, single organ or group of organs is displaced (incomplete situs inversus - ISI, situs ambiguous - SA, heterotaxis - HT) [1-4]. Patient with SIT presents inversed but proper anatomy. However, in 20-25% of SIT cases it coexists with Kartagener Syndrome (immotility of bronchial cilia, bronchiectases, chronic sinusitis, male infertility) [1,3,5-8]. Cardiac, as well as vascular, kidney and intestine defects are more common in SIT patients than in the rest of population [1,3,9-13]. These defects are often revealed in patients with dextrocardia and situs solitus (SS - normal organ position) [3,9]. Dextrocardia, right-sided aortic arch

and double aortic arch, complete and incomplete vascular rings, asplenia and polysplenia syndrome (right and left isomerism) belong to the ISI/SA/HT syndromes [1-3,14,15]. Aristotle was the first to describe SA syndrome (384-322 BC). SIT was first described by Fabrizio in 1600. The famous patient representing SIT was French Queen Maria of Medici (1573-1642) [1,2,16].

REVIEW

Epidemiology and pathogenesis

SIT is a rare autosomal recessive disease [5,6,11,17]. It is probably associated with X chromosome defect and its possible familial occurrence with varying expression [1,4,6,17-20]. The

occurrence rate varies. Kodama et al. [21] assess it as 1:4000 to 1:12000 of births but Inoue et al. [7] as 1:30000 to 1:60000 of births. Majority of authors describe it as 1:8000 to 1:20000 of births [1,4,8,10,11,21-23]. Cilia motility disorder provokes improper extra embryonic fluid flow and false heart tube rotation during embryogenesis, which probably results with SIT [1,6,8,9,17]. The new definition of this process describes cilia rotation motility disorder, that makes nodal flow disturbance in ventral node at the time of gastrulation [24,25]. This genetically driven process can be possibly triggered by some external factors [1,10,13,26]. This issue seems even more complicated, as ciliary dyskinesia syndrome without situs inversus, as well as, SIT cases without ciliary dyskinesia were described. Moreover, there are many cases of ISI with different expression of situs inversus seen even in twins [1,6,17,18,20,27,28]. It is suspected, that there is a correlation between SIT and carcinoma or multiple neoplasms [12,24]. Proper function and structure of cilia is based on intracellular protein pump KIF3, dysfunction of which is observed in ciliary dyskinesia. KIF3 dysfunction blocks N-cadherin/beta-catenin system, which is important in cellular adhesion and proliferation control. Adhesion and proliferation play a key role in the development and progression of neoplasms. A hypothesis has been set that KIF3 dysfunction might be common for SIT and neoplasms [24,25,29-35]. There are many papers describing neoplasms concomitant with SIT [4,13,26,36,37], however, the correlation of SIT and neoplasm is not yet widely accepted and demands further clinical and epidemiologic investigations [13].

Clinical features and diagnostics

The diagnosis of dextrocardia is often confirmed in childhood or adulthood after medical examination and chest X-ray. The CT scan and ultrasonography help to set the exact diagnosis. Sometimes SIT is diagnosed in the elderly patients, who did not have these examinations before [1,9]. The majority of patients described in this paper was admitted to hospitals with diagnosed SIT and were of advanced age. The leading disease symptoms were cough, hemoptysis, loss of weight and chest pain. One patient suffered from the Superior Vena Cava Syndrome (SVCS), and two others were admitted on the basis of radiographic findings without any clinical symptoms. The range of used diagnostic tools, reflects the progress of radiology and oncology within the last 60 years. Patients evaluated in 1960 were diagnosed by: chest X-ray, bacteriology, sputum cytology, bronchofiberscopy, supraclavicular lymph node surgical biopsy (Daniels procedure) and tuberculin test. The more recent patients of the group were diagnosed by contrast enhanced chest CT, transbronchial needle aspiration biopsy (TBNA), FDG - Positron Emission Tomography/CT and serum level of Carcinoembryonic Antigen (CEA) and CYFRA-21 neoplasm biomarkers. Generally bronchofiberscopy and contrast enhanced chest CT are considered to be sufficient to assess the

anatomy and operative conditions, but echocardiography and abdominal ultrasonography were supplemental examinations describing potential anomalies and defects [7,8,12,38]. Subotich et al. [9] applied aortography and pulmonary artery contrast examination additionally. The recent SIT studies advocate the use of three-dimensional CT or Magnetic Resonance Imaging (MRI) reconstruction [13,39-41]. However, the most important diagnostic milestone, is the primary proper interpretation of the chest X-ray in SIT patients [1,3,22].

Publications

Twenty-one cases of lung cancer with SIT, including 2 Polish cases from the authors' center (Department of Thoracic Surgery, Pomeranian Medical University in Szczecin, Poland), were found in the available literature [3,7-9,12,21,22,38,40,42-49]. The first reports were found in 1952 [22] and 1963 [43]. Thirteen cases came from Japan, 4 from Eastern Europe, 2 from Western Asia, and 1 from Australia and USA each. There was one case of SVCS with left main bronchus infiltration [44]. The first case of the lung cancer operation in SIT patient was published in 1990 [21]. There are 13 descriptions of lung cancer operations in SIT patients in total [3,7-9,21,24,38,40,46,48,49,62].

Material

We analyzed a cohort of 21 patients with lung cancer and SIT. There were 20 males and 1 female. The mean age of patients was 68.0 ± 7.7 years. Six of them (6/21-28.5%) presented Kartagener Syndrome. There were 14 left and 7 right lung cancer cases. Majority of them (8/21-38%) was diagnosed as squamous cell carcinoma. Thirteen patients underwent surgery, 3 on the right side and 10 on the left side. One upper lobectomy, 1 lower lobectomy and 1 explorative thoracotomy were performed on the right side. The following surgeries were performed on the left side: 3 pneumonectomies, 4 upper lobectomies, 1 lower bilobectomy, 1 lower lobectomy and 1 middle lobectomy. One patient underwent additional right laparoscopic adrenalectomy. Eight patients were treated without surgery. Five patients had undergone adjuvant therapy, 4 symptomatic therapy, and one patient's therapy was unknown. Data regarding the patients' smoking habits were not available. The patients' characteristic is shown in *Tab. 1*.

Surgery of SIT patients with lung cancer

The proper preoperative assessment warrants the operation safety. In the abdominal emergency operations the knowledge of anatomical anomaly is crucial to prevent operative complications and proper choice of the surgical approach i.e. appendectomy and cholecystectomy [22]. The treatment of all lung cancer/SIT patients was elective and the proper preoperative diagnostics was applied [3,7-9,21,24,38,40,48]. The left sided operations were radical and one right side

Table 1. Characteristics of patients.

nr	author	edited	sex	age	side	treatment	situs	histology
1	Baruah	1952	M	52	right	symptomatic	Kartagener S.	SCLC
2	Thompson	1963	M	58	right	symptomatic	SIT	undefinite
3	Stastny	1967	M	60	left	symptomatic	SIT	SCLC
4	Kawanishi*	1980	M	57	left	pneumonectomy	Kartagener S.	NSCLC(s)
5	Kodama	1990	M	68	left	middle lobectomy	SIT	NSCLC(s)
6	Hachiya	1993	M	71	right	symptomatic	Kartagener S.	NSCLC(s)
7	Higashi*	1994	M	77	left	chemotherapy	Kartagener S.	SCLC
8	Modi	2004	M	68	left	unreported	SIT	NSCLC
9	Subotich	2006	M	71	left	upper lobectomy	SIT	NSCLC(a)
10	Bougaki	2007	M	74	left	upper lobectomy	SIT	undefinite
11	Koichi	2008	M	72	right	upper lobectomy	SIT	NSCLC(s)
12	Murakawa	2009	M	74	left	upper lobectomy	SIT	NSCLC(s)
13	Rahimi-Rad	2009	M	59	left	conservative	SIT	SCLC
14	Bielewicz	2009	M	74	left	lower bilobectomy	SIT	NSCLC(s)
15	Horie	2010	M	71	right	chemoradiation	Kartagener S.	NSCLC(s)
16	Haruki	2010	M	79	right	explorative thoracotomy + chemotherapy	SIT	NSCLC(a)
17	Hino	2010	M	58	left	upper lobectomy	SIT	NSCLC(a)
18	Inoue	2011	M	65	left	pneumonectomy	Kartagener S.	NSCLC(s)
19	Shimizu	2011	F	76	left	lower lobectomy + chemotherapy	SIT	NSCLC(as)
20	Wojcik	2012	M	69	left	pneumonectomy + adrenalectomy + chemotherapy	SIT	NSCLC(l)
21	Yoshida	2012	M	74	right	lower lobectomy	SIT	NSCLC(a)

SCLC – small cell lung cancer; NSCLC – non-small cell lung cancer; NSCLC(s) – squamous cell carcinoma; NSCLC(a) – adenocarcinoma; NSCLC(l) – large cell carcinoma; NSCLC(as) – adenosquamous cell carcinoma

* The cases No 4 and 7 are cited by Inoue et al. [7]

explorative thoracotomy was performed. In all cases, the lungs and the mediastinum had the anatomical features of the opposite side in the description of the operative field. It referred also to the typical variation of the interlobar fissures, bronchial tree and pulmonary vessels. Ten thoracotomies and two video assisted (VATS) approaches were performed [3,8,9,21,24,38,40,48,49]. In one case, median sternotomy was applied to warrant the safety of the left pulmonary vessels preparation. Due to technical conditions, left pneumonectomy was performed and no other vessel anomalies were described [7]. During the only right sided explorative thoracotomy no other surprising vascular anomalies were found [24]. All authors confirmed consistency of the contrast enhanced chest CT with the anatomical conditions found during the operation. No major intraoperative complications were registered due to extraordinary thorough preparation of the vessels and the recurrent nerves [3,7-9,41]. The mirrored anatomy was also seen in the Kartagener Syndrome patients, who were operated on due to bronchiectasis. However, those patients differ according to gender disproportion, presence of bilateral operated patients and pneumonectomy avoidance [6,19,50-58]. The other intraoperative conditions, found relatively often, were: adhesions due to inflammation,

irregularity and broadening of the bronchial arteries, atresia of selected segmental arteries, disease recurrences and reoperations [6,7,19,54,56,59]. The VATS has been already used for the ISI/SIT patients [40,49,60]. Documentation of the lung tumor case with SIT was presented by Diego Gonzales-Rivas [61]. Left-sided minimal invasive middle lobectomy was performed using single small incision. Mirror image of lung anatomy without additional anatomical anomalies and intraoperative troubles was presented.

Own experience

In our study group, two patients were symptomatic and had dextrocardia revealed many years earlier. The diagnostics was based on bronchofiberscopy, abdominal and supraclavicular region ultrasonography, chest, abdominal and head contrast enhanced CT and echocardiography. First patient was a 74-year-old male suffering from SIT and squamous cell left lung carcinoma diagnosed by bronchofiberscopic sample. The left lower lobe bronchus was infiltrated and the bronchofiberscopy showed the right lung anatomy. The preoperative assessments confirmed SIT with no additional anomalies. At the left thoracotomy the right sided anatomy of the lung was observed as expected from the preoperative

findings (Fig. 1). The lower bilobectomy with radical lymphadenectomy was performed and the final staging was stated as pT2N0M0 [3]. Second patient was a 69-year-old male suffering from the left sided non-small cell lung cancer

revealed through sputum cytology. The bronchofiberscopy revealed mirror bronchial anatomy with no intraluminal mass. The preoperative evaluation confirmed SIT and the left lung tumor infiltrating the hilum. Subsequent tumor

Figure 1. a) Middle lobe in the left hemithorax; b) The azygos vein position in the left hemithorax.

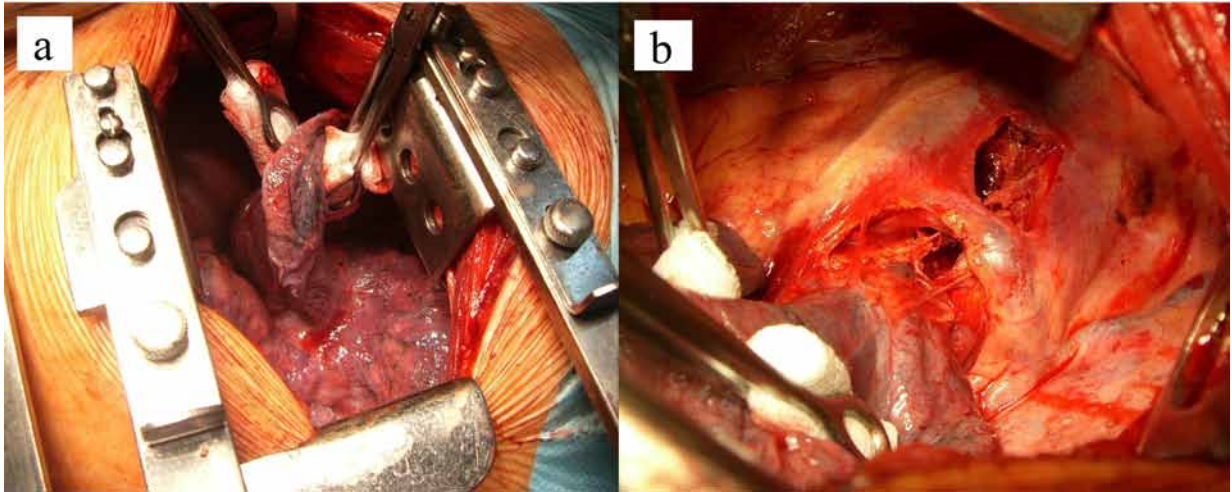


Figure 2. a) Left-sided position of the azygos vein; b) The abdominal mirror image. Enlarged right suprarenal gland.

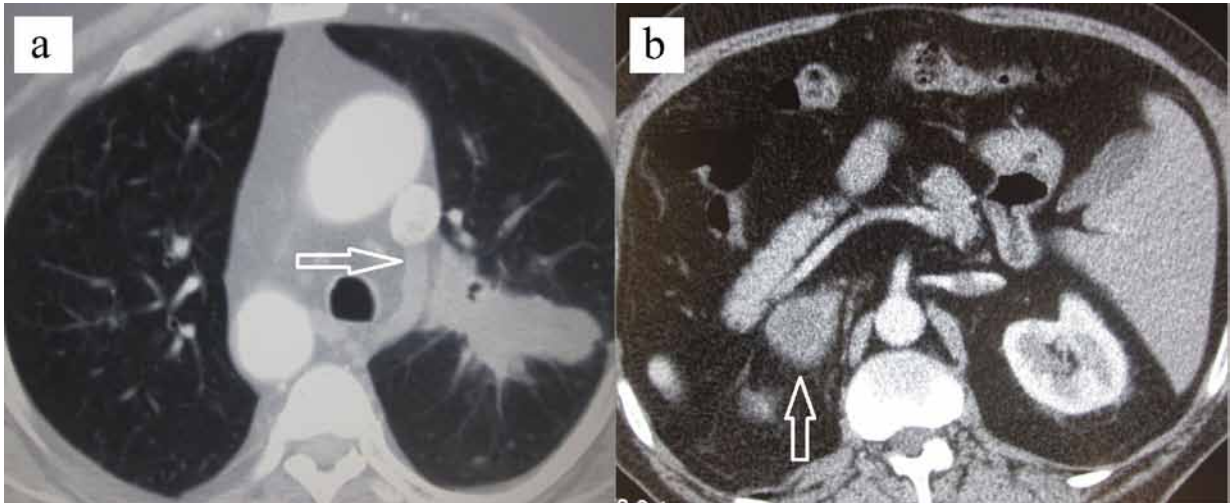
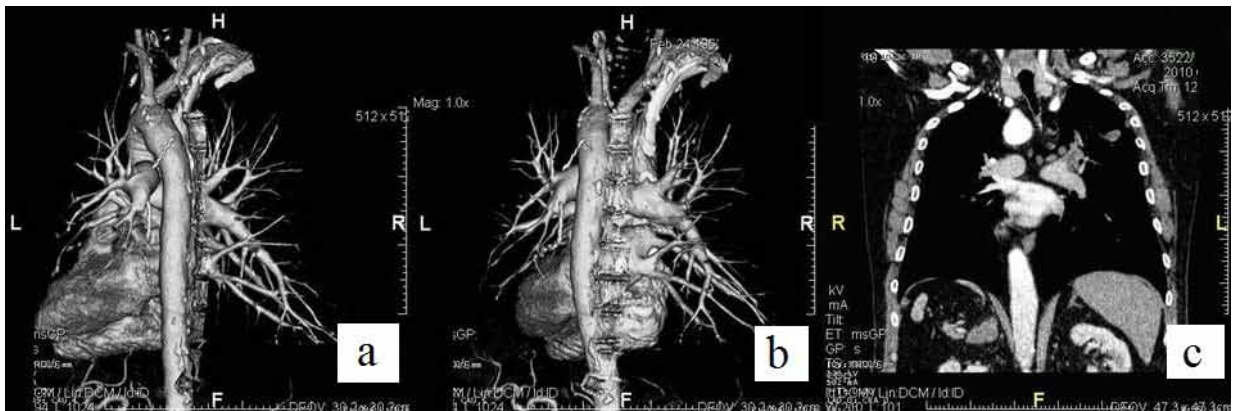


Figure 3. a) and b) (3-D)/CT-angiography of the pulmonary artery; c) Contrast enhanced CT coronal-projection.



(3.8 cm of diameter) of the right suprarenal gland was additionally found. Its malignant, metastatic origin was confirmed by Fine Needle Aspiration Biopsy (FNAB) (Fig. 2). The left thoracotomy showed mirror anatomy of the lung and mediastinum. Pneumonectomy with radical lymphadenectomy was performed. One month later the patient underwent right laparoscopic adrenalectomy and again the intraperitoneal anatomy was also inversed. The final pathological finding stated large cell carcinoma pT2aN0M1. The patient was qualified to adjuvant chemotherapy [62]. Both Polish patients from the authors' center (Department of Thoracic Surgery, Pomeranian Medical University in Szczecin, Poland), were heavy smokers (50 years of smoking, 20 cigarettes daily = 50 packyears). The first patient is still alive in good health and his follow-up reached 65 months. Follow-up of the second patient didn't exceed 12 months.

DISCUSSION

The occurrence of SIT is not consistent in the available literature and ranges from 1:4000 to 1:60000 births [7-9,13,21,24]. In our institution we did not register any concomitance of lung cancer and SIT in 1951-2004, but from 2007 to 2011 two such cases were identified. The SIT occurs more often in Japan and Eastern Europe probably due to demographic reasons [3,7-9,21,24,38,40,42,45,46,48,49,63]. There is a little experience of 21 lung cancer/SIT patients treatment, though the symptoms and the clinical course of the disease is similar to the other lung cancer cases. The most difficult to diagnose and treat are the lung cancer/Kartagener Syndrome patients, as the disease can have the form of recurrent bronchitis and hemoptysis [7]. Surgery qualification for lung cancer/Kartagener Syndrome patients is also difficult because remaining, not resected, bronchiectatic lung tissue can cause a number of postoperative complications. Majority of the study group was male (20/21-95%) though in the previous SIT publications the occurrence of the disease was equally distributed across the gender. The second feature of the study group is the dominance of cases with left-sided lung cancer (14/21-67%) and left-sided surgery (10/13-77%) [3,6-9,21,38,40,46,48,49,62]. Squamous cell carcinoma was the most frequent type of cancer in the study group (8/21-38%), similarly to normal population. Kartagener Syndrome rate in the entire group was higher (6/21-28,5%) than literature rate for such cases (20% - 25%) (Tab. 1) [1,3,5-8]. The available operation descriptions revealed conformity of the operative view with the preoperative contrast enhanced CT and bronchofiberscopy. These data suggest for SIT cases inversed but regular lung anatomy correlated to the preoperative assessment. The inversed, but regular lung and vessel anatomy enabled use of VATS technique [40,49,60,64-67]. Presentation of Diego Gonzalez-Rivas [61] confirms these arguments. The additional preoperative evaluation of

the aortic arch and pulmonary artery is proposed by some authors due to the increased risk of the vessel defects in ISI/SIT syndrome and introduction of VATS technique [8,9]. The 3-D reconstruction of the CT and MRI images is helpful and can be recommended for the future. (Fig. 3) [8,13,39,40,41,67-77]. In some cases of inconclusive CT image, clinical state and blood flow assessment by the additional angiographic evaluation may be necessary [56,78]. Evaluation of ISI by means of EBUS, EUS and mediastinoscopy makes the surgery safe and should be used in the assessment of SIT [79]. The inversed anatomy of the bronchial tree results in the use of the properly sided double-lumen intubation tube (DLT). The optimal option is the left sided DLT introduced into the right main bronchus, though some authors used the single-lumen tube (SLT) [38,46,48,80]. Our second case is one of the first lung cancer/SIT patients, who underwent laparoscopic adrenalectomy due to lung cancer metastasis. According to progress and former publications it leads to the suggestion, that the SIT patients may be safely operated by VATS and laparoscopy procedures or can even be the donors or recipients in organ transplantation [16,23,71-83].

CONCLUSIONS

We conclude, that lung cancer/SIT cases despite inversed but regular anatomy can be operated on radically as cases with normal anatomy with preservation of intraoperative security level.

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