Advanced surgical technologies for lung cancer treatment

Cai, Hongfei; Wang, Yonghui; Qin, Da; Cui, Youbin; Zhang, Hongbo

Published in:
Engineered Regeneration

DOI:
10.1016/j.engreg.2022.12.001

Published: 01/03/2023

Document Version
Final published version

Document License
CC BY

Engineered Regeneration 4 (2023) 55–67

Contents lists available at ScienceDirect

Engineered Regeneration

journal homepage: http://www.keaipublishing.com/en/journals/engineered-regeneration/

Advanced surgical technologies for lung cancer treatment: Current status and perspectives

Hongfei Cai [a,‡], Yonghui Wang [b,c,‡], Da Qin [a], Youbin Cui [a,*], Hongbo Zhang [b,c,*]

[a] Department of Thoracic Surgery, the First Hospital of Jilin University, 71 Xinmin Street, Changchun 130021, China
[b] Pharmaceutical Sciences Laboratory,Åbo Akademi University, Turku 20520,Finland
[c] Turku Bioscience Centre, University of Turku and Åbo Akademi University, Turku 20520, Finland

ARTICLE INFO

Keywords:
Lung cancer
Surgical treatment
Nanotechnology
Synergistic treatment

ABSTRACT

Lung cancer has become one of the key life-threatening factors and is the most common type of tumor. With the improvement of equipment and the improvement of lung cancer awareness, the surgical treatment of lung cancer is becoming more and more mature. Surgery can provide an important part of individualized treatment strategies for patients with different stages of lung cancer and different wishes. In addition, the concept of minimally invasive, precise, and intelligent has triggered a revolutionary change in the surgical treatment strategy for lung cancer. Therefore, this review focuses on the development of lung cancer surgery history, summarizing the era from traditional surgery to the era of minimally invasive thoracic surgery based on TV-assisted thoracic surgery. The operating methods and treatment effects of different surgical methods are comprehensively introduced, and the optimization and improvement of different surgical methods in the future are also discussed. Along with the concept of minimally invasive surgical techniques, there are more and more explorations of nanotechnology in the surgical treatment of lung cancer. The application of nanotechnology in lung cancer imaging, and the combination of surgery with nanomedicine is an effective solution for cancer treatment today. So, this review also summarizes the application prospects of nanotechnology before, during and after lung cancer surgery.

1. Introduction

The development of lung cancer surgery continues to leap forward with the innovation of surgical techniques and the update of surgical equipment. Its combination with nanotechnology is also one of the hot spots in the existing research.

1.1. History and status of lung cancer surgery

Lung cancer has the highest mortality in the world population, and the incidence rate ranks second. According to the 2020 Global Cancer Statistics, lung cancer accounts for 11.4% of all new cases and 18% of all cancer deaths [1]. Meanwhile, in both developed and developing countries, lung cancer has been the largest contributor to the cancer medication burden [2]. Early-stage lung cancer has increased detection rates on low-dose thin-section CT scans, especially in non-smoking Asian females. Although the incidence is still twice as high in men as in women, the incidence of lung cancer is increasing in women and decreasing in men [1,3]. The first choice for patients with lung cancer of clinical stage I or II is surgery [4]. For locally advanced NSCLC, neoadjuvant therapy is recommended for selected patients [5]. So, surgery remains an essential part of lung cancer treatment.

Since the first pneumonectomy for lung cancer was reported successfully by Graham et al in 1933 [6], the surgical methods and techniques for lung cancer have been continuously developed. The emergence of video-assisted thoracoscopic surgery (VATS) in the 1990s is a major technological revolution in the field of cardiothoracic surgery. In 1992, Roviaro et al first reported VATS anatomical lobectomy [7], which opened a new chapter of VATS in the surgical treatment of lung cancer. In 2006, the NCCN guidelines included VATS radical resection of tumor side as the standard way for patients treatment [8]. In the past few years, minimally invasive surgery for lung cancer has made great progress in terms of the size and number of incisions, the extent of resection, and total body response to surgery. Lung cancer surgery continues to develop from traditional thoracotomy to minimally invasive thoracic surgery to precision treatment, which is at the forefront of surgical innovation. Table 1 lists the important events in the history of lung cancer surgery, which proves that lung cancer surgery has become a mature clinical discipline.

* Corresponding authors.
E-mail addresses: cuiyb@jlu.edu.cn (Y. Cui), hongbo.zhang@abo.fi (H. Zhang).
‡ Equal contribution.

https://doi.org/10.1016/j.engreg.2022.12.001
Received 17 October 2022; Received in revised form 1 December 2022; Accepted 1 December 2022
Available online 2 December 2022

Table 1
The important events in the history of lung cancer surgery cancer surgery.

Year	Authors	Event
1933	Evarts A. Graham and J. J. Singer	The first radical resection of lung cancer was completed via a left pneumonectomy. [6]
1947	Sir Clement Price Thomas	The first reported bronchial sleeve resection was performed at the Brompton Hospital in London, England. [9]
1962	Shimkin MB, Connelly RR, Marcus SC, et al.	Comparing case series of pneumonectomy and lobectomy showed that survival after lobectomy was equivalent to pneumonectomy with fewer complications. [10]
1973	Jensik RJ, Faber LP, Milloy FJ, et al.	Anatomical segmentectomy for lung cancer was first described. [11]
1992	Lewis RJ, Caccavale RJ, Sisler GE, et al.	Video-assisted thoracoscopic surgery (VATS) lobectomy is used in the treatment of lung cancer. [7]
2006	Petersen RP, Pham DK, Toloza EM, et al.	The feasibility of VATS lobectomy for the management of locally advanced disease after induction therapy was first described. [12]
2007	Swanson SJ, Herndon JE II, D'Amico TA, et al.	The definition of VATS lobectomy was established in a prospective, multiinstitutional study. [13]
2011	Gonzalez D, Paradela M, Garcia J, et al.	Uniportal VATS lobectomy for lung cancer surgery was first described. [14]
2011	Chen JS, Cheng YJ, Hung MH, et al.	Nonintubated thoracoscopic lobectomy for lung cancer was described. [15]
2012	Cao C, Manganas C, Ang SC, et al	Robotic video-assisted thoracic lobectomy for lung cancer was described. [16]
2015	Li M.	The world's first radical resection for lung cancer using glasses-free 3D thoracoscope was completed. [17]
2017	Abbas A, Kadakia S, Ambur V, et al.	The use of electromagnetic navigational bronchoscopic localization of nodules by injecting them with indocyanin green (ICG) was first reported [18].

1.2. Nanotechnology in lung cancer treatment

As we all know, surgery, as the main means of solid tumor resection, is the main choice for tumor treatment today. However, more and more postoperative reports show that no matter what kind of tumor, the incidence of postoperative recurrence or metastasis is very high, and the long-term survival is not ideal [19]. In order to maximize the effect of surgical treatment and reduce the probability of recurrence, two main points need to be considered. First, in the clinical concept, complete resection does not imply infinite enlargement of the surgical margins. The area of surgical resection should be based on the situation of different patients, and then specify the boundaries of surgical resection. Second, surgery is the macroscopic resection of the tumor, limited to the elimination of MRD [20]. Theoretically, complete removal of lesions through "complete resection" can effectively prevent recurrence and metastasis due to tumor dissemination. However, how to achieve "complete excision"? This is a conundrum that has puzzled oncologists and researchers for nearly two centuries. Therefore, more focus should be on adjuvant strategies for synergistic anticancer effects. The development of new technologies has brought new hope to the era of precision surgery in the 21st century, which is dominated by precise tumor resection.

In the assessment of whether sufferer with lung cancer need or can undergo surgical treatment, many imaging techniques need to be used to determine the location, size, and structure of the tumor to evaluate the possibility and risk of surgery. Imaging techniques commonly used in clinical practice include CT, MRI, and PET/SPECT. Based on the imaging results of these imaging techniques, patients can be treated comprehensively before, during, and after surgery [21]. Among them, the most critical is postoperative evaluation, mainly the evaluation of residual areas and surgical complications to predict the probability of postoperative recurrence. In generally, the more complete the surgical resection of the tumor site, the lower the probability of postoperative recurrence. However, even in today's era of precision surgery, conventional intraoperative imaging technologies such as CAS cannot achieve real-time precision image-guided surgery (IGS). Therefore, the tumor site cannot be displayed to the maximum extent, so that 80% of the tumor cannot be removed. In the actual operation process, the surgical resection boundary is estimated more relying on the surgeon's experience and spatial imagination. Therefore, postoperative recurrence rate is high, and surgical complications are serious, leading to organ dysfunction, failure, and even death. Fortunately, molecular imaging technology is constantly evolving according to clinical needs, more and more researchers are committed to developing IGS technology, and more and more IGS technology is applied in clinical practice, promoting the development of biomedical therapeutic diagnosis and application. And with the development of nanotechnology, nanomaterials (NMs) for IGS highlight the advantages of nanotechnology in synergistic cancer therapy [22]. The application of NM in clinical surgery is attributed to its high resolution and deep tissue penetration properties, which can make up for the shortcomings of existing devices. In addition, multifunctional NMs can interact with other adjunctive therapies such as chemotherapy, immunotherapy, and phototherapy to achieve the elimination of the residual disease.

The clinical application of nanotechnology, especially the further development of NM in the treatment of multimodal IGS-assisted precision surgery. In precision image-guided surgery, all nanoformulation contrast agents can passively accumulate into the tumor site based on the enhanced permeability and retention (EPR) effect. In addition, nanocontrast agents also show a unique advantage, that is, they can be expressed according to the specific and highly expressed receptors of lung cancer or other tumors. Then, specific matching receptors are linked to the surface of the nanodeveloping agent, and through ligand-receptor interaction, it can be specifically targeted and accumulated to the tumor site. Not only the concentration of the contrast agent at the tumor site can be increased, but also the accumulation in normal tissues can be reduced, reducing side effects. In addition, with different design methods, the

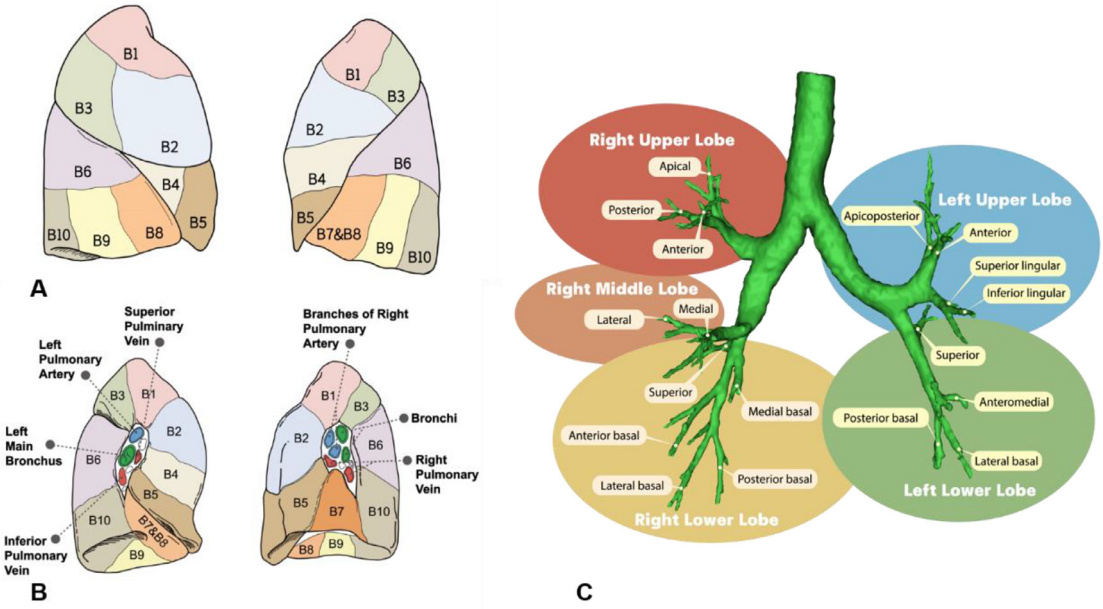

Fig. 1. A: Lateral view of the bronchopulmonary segments for both the right and left lung (Draw from author). The key for the numbering system appears in Table 2; B: Medial view of the bronchopulmonary segments of the right and left lung with the hilar structures labeled. Note the relationships at the hilum of the bronchovascular structures (Draw from author); C: Segmental anatomy of the bronchial tree (Draw from author).

size of nanoparticles can be flexibly adjusted, from large size to small size, which increases the penetration ability inside solid tumors and enables more contrast agents to be dispersed to the tumor edge area, which greatly improves the Accuracy of preoperative tumor detection and intraoperative tumor margin delineation. Nanoparticles can be engineered into multifunctional therapeutic and diagnostic nanoplatforms that combine imaging and navigation capabilities with other treatments to create diagnostic-therapeutic-integrated nanoplatforms, in which complete tumor resection at the macroscopic level can be achieved to help patients get rid of cancer [23,24]. Surgery combined with nanotechnology opens up a promising approach for tumor therapy in the new century.

2. Basic knowledge of lung cancer surgery

Pulmonary anatomy is the most basic knowledge that pulmonary surgeons need to be proficient in, which includes the adjoining relationships of pulmonary arteries, pulmonary veins, and airways. And for different stages of lung cancer, different treatment modalities are available. The following are the essential knowledge of lung cancer surgery.

2.1. Lung anatomy

The bronchopulmonary segment is the most anatomic, surgical, and pathologic unit of the lung that is most important. Boyden described segmental anatomy in all its complexity in his classic Segmental Anatomy of the Lungs, published in 1955. The bronchopulmonary segments are detailed in Fig. 1 and listed in Table 2.

2.2. Lung cancer classification and grading

In lung cancer, its biological behavior, treatment and prognosis are different, and WHO divides it into two categories: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). NSCLC accounts for more than 80% of all lung cancers. NSCLC can be further divided into adenocarcinoma, squamous cell carcinoma, large cell carcinoma and other subtypes. Among smokers, the most common cause is lung adenocarcinoma.

Table 2
Bronchopulmonary segment.

Bronchopulmonary segments
Right Upper Lobe
1. Apical 2. Anterior 3. Posterior
Right Middle Lobe
4. Lateral 5. Medial
Right Lower Lobe
6. Superior 7. Medial basal 8. Anterior basal 9. Lateral basal 10. Posterior basal
Left Upper Lobe
1 and 3. Apicoposterior 2. Anterior 4. Superior lingular 5. Inferior lingular
Left Lower Lobe
6. Superior 7 and 8. Anteromedial 9. Lateral basal 10. Posterior basal

In the eighth edition of TNM Definitions and Staging (Tables 3 and 4), the International Association for the Study of Lung Cancer (IASLC) further revised the lung cancer staging system, which was subsequently accepted by the American Cancer Society (AJCC) [25]. Therefore, the current clinical grading of carcinoma of the lungs TNM is as follows: early-stage is stage I and stage II with negative lymph nodes; locally advanced is node-positive stage II and III, and advanced or metastatic disease stage is stage IV.

3. Traditional surgical methods and current progress

The beginning of lung cancer surgery is attributed to the development of modern anesthetic techniques. When anesthesia first developed, inhalants such as ether or chloroform can be used in general anesthesia. At this time, the patient had spontaneous breathing. However, when the chest cavity is opened, the resulting pneumothorax rapidly leads to ipsilateral lung failure and paradoxical breathing. So, the patient quickly becomes hypoxic and comatose. Meanwhile, surgery on a ventilated lung can be fully dangerous, and very easy to cause patients dead. In 1909, first described positive pressure ventilation, which can maintain continuous lung ventilation in the case of deep anesthesia and pneumothorax [26]. Then, started the select one-lung for ventilation through contralateral mainstem bronchial intubation. So, the anesthetic techniques ensure the safety of thoracic surgery. After then, the first case of

Table 3
Definitions for TNM descriptors.

T (primary tumor)	
T0	No primary tumor
Tis	Carcinoma *in situ* (squamous or adenocarcinoma)
T1	Tumor ≤ 3 cm
T1mi	Minimally invasive adenocarcinoma
T1a	Superficial spreading tumor in central airways[a]
T1a	Tumor ≤ 1 cm
T1b	Tumor>1 but≤2 cm
T1c	Tumor>2 but≤3 cm
T2	Tumor>3 but≤5 cm or tumor involving: visceral pleura, main bronchus (not carina), atelectasis to hilum[b]
T2a	Tumor>3 but≤4 cm
T2b	Tumor>4 but≤5 cm
T3	Tumor>5 but≤7 cm or invading chest wall, pericardium, phrenic nerve; or separate tumor nodule(s) in the same lobe
T4	Tumor>7 cm or tumor invading: mediastinum, diaphragm, heart, great vessels, recurrent laryngeal nerve, carina, trachea, esophagus, spine; or tumor nodule(s) in a different ipsilateral lobe
N (regional lymph nodes)	
N0	No regional node metastasis
N1	Metastasis in ipsilateral pulmonary or hilar nodes
N2	Metastasis in ipsilateral mediastinal or subcarinal nodes
N3	Metastasis in contralateral mediastinal, hilar, or supraclavicular nodes
M(distant metastasis)	
M0	No distant metastasis
M1a	Malignant pleural or pericardial effusion[c] or pleural or pericardial nodules or separate tumor nodule(s) in a contralateral lobe
M1b	Single extrathoracic metastasis
M1c	Multiple extrathoracic metastases (1 or>1 organ)

a: Superficial spreading tumor of any size but confined to the tracheal or bronchial wall.
b: Atelectasis or obstructive pneumonitis extending to hilum; such tumors are classified asT2a if>3 and≤4 cm, T2b if > 4 and ≤ 5 cm.
c: Pleural effusions are excluded that are cytologically negative, nonbloody, transudative, and clinically judged not to be due to cancer.

Table 4
AJCC prognostic groups.

	T	N	M
Occult Carcinoma	TX	N0	M0
Stage 0	Tis	N0	M0
Stage IA1	T1mi	N0	M0
	T1a	N0	M0
Stage IA2	T1b	N0	M0
Stage IA3	T1c	N0	M0
Stage IB	T2a	N0	M0
Stage IIA	T2b	N0	M0
Stage IIB	T1a/T1b/T1c/T2a/T2b	N1	M0
	T3	N0	M0
Stage IIIA	T1a/T1b/T1c/T2a/T2b	N2	M0
	T3/T4	N1	M0
	T4	N0	M0
Stage IIIB	T1a/T1b/T1c/T2a/T2b	N3	M0
	T3/T4	N2	M0
Stage IIIC	T3/T4	N3	M0
Stage IVA	Any T	Any N	M1a/M1b
Stage IVB	Any T	Any N	M1c

pneumonectomy opens a new era of thoracic surgery, which was accomplished by Dr. Evarts Graham to detach the tumor in the lobus superior pulmonis sinister [6]. With the progress of medical technology, video-assisted thoracoscopic surgery (VATS) lobectomy has been accepted by more doctors and has gradually become the standard operation for early-stage lung cancer. At the same time, more and more early-stage lung cancer cases had been detected because of the wide application of low-level exposure CT sifting. However, predominate of lung cancer cases are still in an advanced stage. If patients developed centrally located NSCLC, sleeve lobectomy became the preferred procedure. Some patients with locally advanced disease may perform incorporated surgery remove of the primary tumor and involvement of adjacent structures if necessary. So, traditional thoracotomy is still an indispensable part of lung cancer surgery. Below will a review of the modern surgical practice of patients with lung cancer located in the center, or invading neighboring structures which include the tracheal carina, chest wall, superior vena cava, and aorta.

3.1. Centrally located NSCLC

In cases where the tumor expands from the lobar bronchus to the main bronchus, the surgeon may remove a section of the main bronchus that is continuous with the affected lobe as an alternative to total pneumonectomy. This procedure is known as sleeve resection, and it conserves the ipsilateral lung parenchyma. Sleeve lobectomy is a method of removing the affected lobe of the lung and part of the main stem bronchus. The residual lobe is replanted into the main stem bronchus. ERINO A. et al. [27] summarized some technical points about sleeve lobectomy and pulmonary artery reconstruction: 1) the anatomy of the anastomosis should be delicate and all margins should be examined by frozen sections; 2) the anastomotic suture should be well protected by vascular tissue; 3) the use of low-dose steroids help to decrease bronchial anastomotic edema; and 4) cautious selection of PA reconstruction technique(end-to-end, patch, conduit) is essential to avoid kinking or stenosis of the PA, which may affect blood flow and create the risk of PA thrombosis. In 1999, extended sleeve lobectomy (ESL) was originally characterized as a lung resection of more than 1 lobe with atypical bronchiectomy and reconstruction. In comparison to standard sleeve lobectomy, ESL may present some technical difficulties, such as variable bronchial caliber size, anastomotic site tension, and more frequent joint angioplasty. But with the development of thoracic surgical technique, sleeve resection combined with pulmonary artery reconstruction has become a routine operation for centrally located NSCLC.

3.2. Locally advanced NSCLC

For locally advanced NSCLC, it is essential to perform en bloc resection of cancerous tissue. When removing the adjacent tissues, it is sometimes necessary to reconstruct the related tissues. For invasive superior vena cava or aorta, the choice of vascular resection and reconstruction performed depends on the extent of vessel involvement [28]. Meanwhile, cardiopulmonary bypass (CPB) expands the surgical indications of extended resection of lung cancer and ensures the safety of the operation.

For invading chest wall, the reconstruction is indicated by the following conditions: the defect of chest wall which is not covered by the scapula includes the removal of more than three ribs or an area of at least 4.0*4.0 cm [29]. For invading tracheal carina, it is generally believed that the length of the resection carina should be less than 4cm, the length of the lower trachea should not be more than 1cm, and the anastomosis can be covered with intercostal muscle flap and pleura, which plays an important role in reducing anastomotic complications.

4. Emerging surgical methods and achievements

With the improvement of surgical skills and the upgrading of surgical instruments and auxiliary facilities, lung cancer surgery has started to pursue minimally invasive and precise while ensuring complete resection, which is the result of the popularization of CT and the inevitable development of surgical procedures.

4.1. Minimally invasive thoracic surgery

In the past, the standard surgical procedure for thoracic tumors has always been thoracotomy. At the end of the 1990s, video-assisted thoracoscopic surgery developed rapidly due to minimally invasive surgery

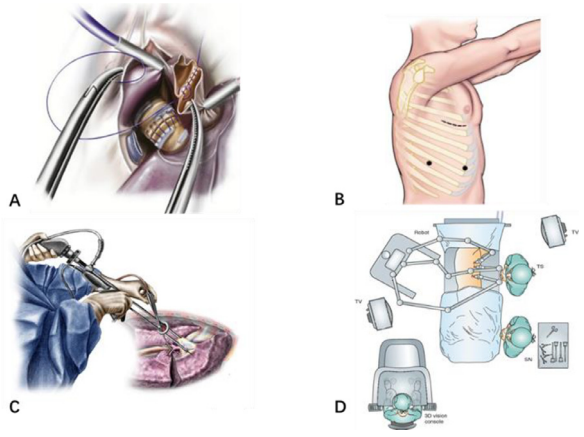

Fig. 2. A: Sleeve resection and end-to-end anastomosis of the pulmonary artery (Copyright © Elsevier and Copyright Clearance Center) B:3-port VATS incision diagrammatic sketch (Redraw from [37]) C: uniportal VATS incision diagrammatic sketch (Redraw from [38]); D: Operating room configuration for robotic lobectomy (Redraw from [39]).

and became another option for early non-small cell lung cancer surgery. Since then, significant advances in the technical aspects of surgery have been made. Changes of the surgical incision, robot-assisted thoracoscopic surgery (RATS), and non-intubation anesthesia are all parts of minimally invasive surgery (MIS).

4.1.1. Video-assisted thoracoscopic surgery

According to statistical data in the past two decades, VATS can significantly shorten the hospital stay of postoperative patients, reduce the incidence of complications, and improve the long-term survival rate of patients compared with traditional thoracotomy [30,31]. With increasing evidence of oncologic equivalence and reports of minimally invasive procedures, VATS lobectomy has been the preferred strategy for the resection of early-stage lung cancer at many institutions.

VATS is divided into two forms, one is hybrid VATS, and the other is complete VATS. In hybrid thoracic surgery, video-assisted minithoracotomy is widely promoted, in which surgeons perform a small thoracotomy approximately 10 cm in length while using direct observation of the incision and video monitor imaging. In complete VATS, the surgeon usually makes three or four small incisions to monitor the procedure. Swanson et al. [13]. defined VATS lobectomy by summarizing the relevant literature. The following definition is widely accepted as the norm to date:

1) No expansion of the rib cage
2) Maximum length of the incision is 8 cm
3) Separate stripping of veins, arteries and trachea of the associated lobe
4) Standard lymph node sampling or dissection.

In the early stages of the development of thoracoscopic surgery, multi-port is a mainstream procedure, with one port for the camera and an additional port for the instrument, called the traditional three-port VATS (Fig. 2A-B) [32]. With the proliferation of thoracoscopic techniques and instruments, doctors are more focused on reducing surgical trauma, so reducing the number of ports becomes a hot spot. Naturally, the back-end port was omitted, resulting in the dual-port VATS technology, mainly consists of one camera port and one utility port [33]. The camera port was therefore eliminated and the surgeon could place the camera directly in the utility port for better ergonomics and visualization, which was later referred to as single-port VATS (Fig. 2C). Since the beginning of the uniportal method for VATS lobectomy in 2010, this technology is widely used all over the world, largely due to the reduced opportunity for incision trauma. Meanwhile, the development of this technology has also benefited from the update of some instrument such as higher resolution cameras, more flexible surgical instruments, and more angled stapling devices [14]. Undoubtedly, China has been the most receptive to this technology, and a large number of operations has allowed for its rapid acquisition and dissemination [34]. Another common single-port VATS is the subxiphoid single-port VATS, which can effectively reduce the incidence of postoperative intercostal neuralgia [35]. However, it is still too early to declare the superiority of single-port VATS in lung cancer surgery. A higher level of evidence is required, in particular in terms of surveying the objective benefits and treatment outcomes of the single-incision approach [36].

4.1.2. Robot-assisted thoracoscopic surgery

In recently years, robotic-assisted surgery has been introduced into thoracic surgery to resolve some of the technical limitations of thoracoscopic surgery. Estimated benefits including improved maneuverability with limited VATS instrumentation and superior imaging through high resolution video of the surgical area represent a technological development in the MIS method [40]. When doctors are proficient in robotic surgery, they can get the same visual experience as thoracotomy. This is why robotic lung surgery is called "virtual thoracotomy" [41]. The space layout of RATS is shown in the Fig. 2D. RATS is frequently used successfully for most of difficult thoracic surgery including sleeve lobectomy, pneumonectomy, chest wall resection, tumor resection after neoadjuvant radiochemotherapy [42]. In addition, RATS provides a platform to add some additional techniques for instance image overlay and navigation aids. It has been reported that nodules are localized during robotic lung surgery by injecting indocyanine green (ICG) and using electromagnetic navigation bronchoscopy [18]. The latest development is the emergence of single-port and robot-assisted thoracic surgery with the upper abdominal approach. However, the high start-up cost of robotic surgery has discouraged many patients. It is hoped that the long-term benefits of robotic surgery for patients and the reduction in startup costs will allow the technology to become more widely available in the future.

4.1.3. Nonintubated anesthesia for thoracoscopic surgery

Traditional VATS require surgery under general anesthesia with double-lumen endotracheal intubation and one-lung ventilation. Adverse reactions and complications of one lung ventilation after general anesthesia intubation are unavoidable, mainly including intubation related trauma, lung injury caused by ventilator, atelectasis, postoperative nausea and vomiting because of the narcotic [43]. In order to prevent the side effects of general anesthesia, non-intubated thoracoscopic surgery has been used for simple operations, such as pneumothorax, pulmonary nodules or lymph node biopsy [44,45]. With the further improvement and exploration of non-intubation technology, as the standard operation for early lung cancer, anatomical lobectomy combined with mediastinal lymph node dissection can be successfully completed under spontaneous respiration that does not trigger a coughing response during traction lung parenchyma and hilar manipulation. Some studies have also proved that this technique does not increase the occurrence of perioperative complications and it can shorten the hospital stay and accelerate postoperative recovery. As a result, non-intubated VATS has been widely used for standard procedures for lung cancer (Fig. 3) [15,46,47]. Recently, a new type of thoracic surgery, called “tubeless surgery”, has been developed for the surgical removal of small peripheral pulmonary nodules. In this innovation, neither intraoperative tracheal intubation nor postoperative chest tube are necessary [48].

4.2. Precision treatment

With the popularity of Computed Tomography, lung nodules mainly composed of ground glass have been widely found. Such nodules are generally difficult to be impalpable during surgery, so accurately locating pulmonary nodules is a challenge for thoracic surgeons. So, it is essential to develop accurate and efficient tumor localization, precision

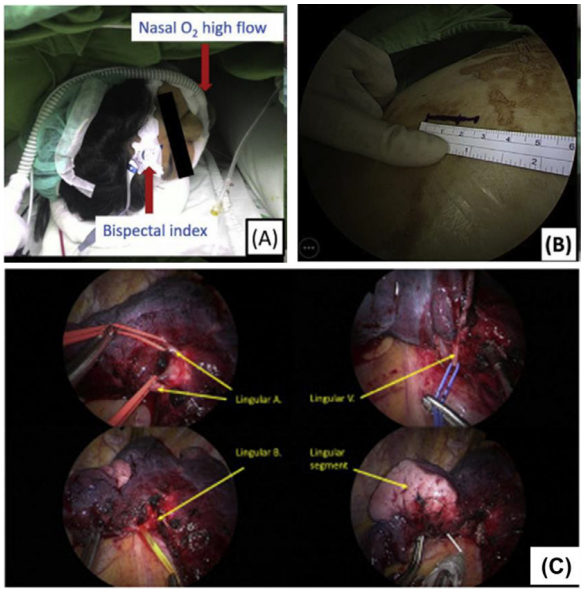

Fig. 3. Nonintubated uniportal thoracoscopic surgery. A: Detection of patients by bispectal index and simultaneous administration of high-flow transnasal assisted ventilation; B: Preoperative surgical incision planning; C: Intraoperative anatomical marking of the arteries and veins of the pulmonary segment (Copyright Elsevier and Copyright Clearance Center).

thoracoscopic segmental resection, and application of 3D technology for early lung cancer surgery.

4.2.1. Tumor localization

With the advancement and popularization of lung cancer screening technology, the ability to distinguish benign and malignant pulmonary nodules has been continuously improved, especially in the early detection of lung cancer. However, these nodules are usually characterized by small diameter, pure ground glass or partially ground glass, and deep position, so it is difficult to detect during operation. Thus, it is particularly important to localize small pulmonary nodules before surgery. There are several different ways of localization, including CT-guided percutaneous, bronchoscope-guided percutaneous, and CT virtual 3D positioning. Targets placed by bronchoscopy or percutaneous puncture have been used around the world. CT-guided hook-wire localization procedures are shown in Fig. 4A-C. Virtual-assisted lung mapping (VAL-MAP) involves the use of multiple dye markers applied to the surface of the lung via bronchoscopy. VAL-MAP is a "mapping" technique that shows the specific area to be resected, rather than "marking" the proximal pleural surface to be resected (Fig. 4D). Electromagnetic navigation bronchoscopy (ENB) is an image-guided procedure based on three-dimensional reconstruction of CT scan and sensor localization. It uses steerable endoscopic probes and three-dimensional reconstruction of the lung to guide routine bronchoscopy to reach peripheral unreachable lesions (Fig. 5A). Each has its advantages and disadvantages (Table 5) [49–56].

4.2.2. Precision thoracoscopic segmental resection

In 1973, Jensik and his team described the first anatomical segmentectomy of lung cancer [11]. Anatomical resection of one or more lung segments in a lobe is called a segmental resection. Several early studies suggest that segmental resection is an appropriate treatment for early-stage lung cancer, especially in eligible patients. In 1995, the results of a study showed that the recurrence rate of sublobar resection, especially at the surgical site, was 3 times higher than that of lobectomy, so lobectomy was the standard treatment for early-stage non-small cell lung cancer [57]. However, there is now increasing evidence that there is no significant difference between sublobar resection and lobectomy if one simply focuses on short- and long-term survival of patients [58]. But two prospective randomized controlled trials, called Cancer and Leukemia Group B (CALGB 140503) and the Japanese Clinical Oncology Group (JCOG 0802), are underway to further compare the short- and long-term survival outcomes of these two procedures for a more good clinical guidance [59]. Excitingly, the results of JCOG 0802 have been published in the Lancet, showing overall survival is higher with segmental lung resection than lobectomy in selected NSCLC. So, this trial suggests segmentectomy can be the standard procedure for specific patients [60].

4.2.3. Application of 3D technology

Many hospitals are now using 3D reconstruction techniques to clarify arteriovenous and tumor relationships to guide segmentectomy (Fig. 5B) [61]. 3D printing technology can transform 3D reconstructed images into models on which surgeons can perform the entire surgical steps [62].

In a relatively short period of time, thoracic lung surgery has progressed at an alarming rate. What we need to do is to choose the best treatment according to the patient's actual condition in order to achieve true MIS, that is, to reduce trauma and get better short-term and long-term benefits.

5. Application of nanotechnology in lung cancer surgery

Notably, nanomaterials with excellent functional and structural properties are suitable for precision therapeutic strategies [63]. There is more and more development of modern technology has opened up new methods for the treatment of tumors. Based on the hallmarks of cancer and the physicochemical properties of NMs design nanosystems that will entitle the system to multiply capabilities for precision treatment. Tumor targeting generally divides into two types: passive and active targeting pathways. Passive targeting which is mainly determined by the size of the nanoparticles. Small particles with a particle size of less than 10 nm can freely penetrate through the endothelium of blood vessels and capillaries and then be easily cleared by the kidneys, but particles with larger particle sizes like more than 100 nm with poor endothelial permeability, also easily eliminated by the liver and spleen and clearance by the reticuloendothelial system (RES) [64,65]. Furthermore, if the particles are hydrophilic, which will affect the EPR effect, therefore we can increase water solubility by assembling hydrophilic polymers on the surface of NPs to improve delivery rates and reduce retention in lymphatic vessels at the same time. While the targeting solely depends on passive targeting has low efficiency.

So, based on the tumor-specific receptors that are highly expressed in the tumor cell members, the corresponding ligands can be linked to the surface of the nanomaterials, thereby actively target to the tumor cells [66]. Antibodies, peptides, small molecules, etc. as commonly used ligands [67,68] can specifically target antigens or receptors which are overexpressed in tumors. For example, epidermal growth factor receptor (EGFR) as a hot target protein which is found to be overexpressed in non-small cell lung cancer, as well as other types of cancer, like kidney cancer, and breast cancer, which has become an effective target for the design of lung cancer-targeted nanosystems [69,70]. Furthermore, nanosystems are designed by combining the characteristics of surrounding tissues, immune cells, blood vessels, and extracellular matrix around lung cancer with high specific recognition characteristics, thereby achieving high delivery efficiency. When the nanosystem successfully accumulates and penetrates various parts of lung cancer tissue, it can perform its imaging or therapeutic functions.

5.1. Nanotechnology assists preoperative diagnosis

The key problem facing tumor treatment is how to find, diagnose and treat early. However, current imaging tests such as CT, single photon emission computed tomography (SPECT), positron emission computed

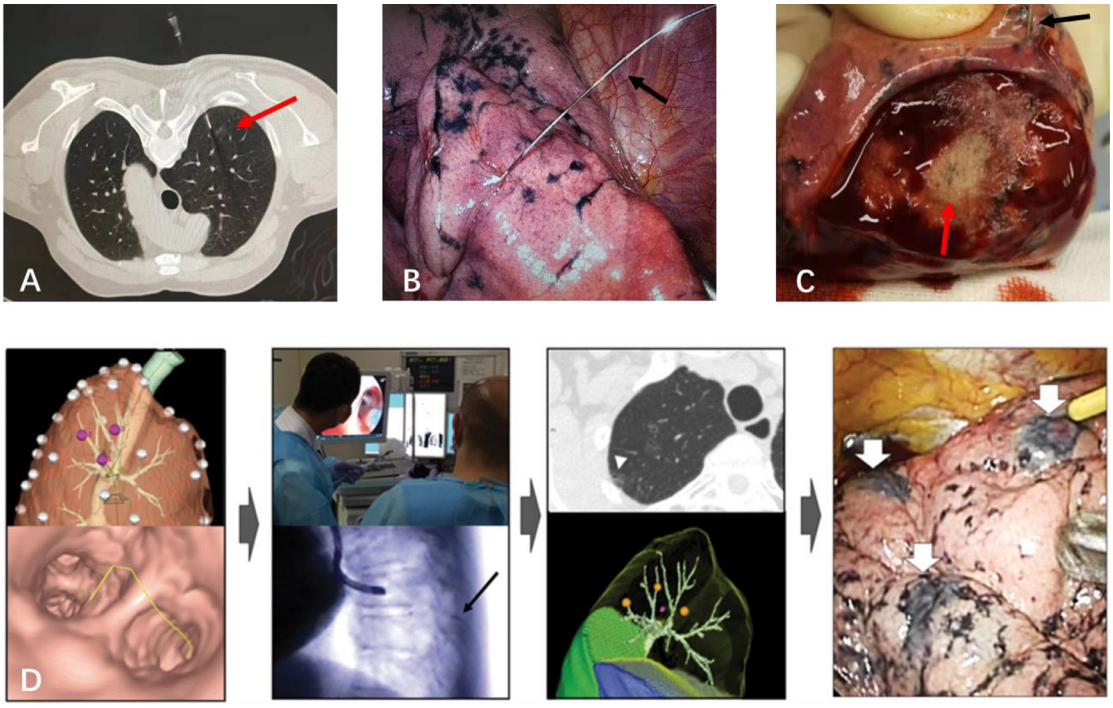

Fig. 4. A-C (Draw from author): Computed tomography-guided hook-wire localization. A: Preoperative CT was performed to determine the puncture site; B: Lesion localization during operation; C: Lesion after pulmonary wedge resection; Red arrows: Lesion location; Black arrows: hook-wire location; D: Implementation process of VAL-MAP: The staining mark during operation is realized by preoperative 3D image and virtual bronchoscope (Copyright The Author 2016).

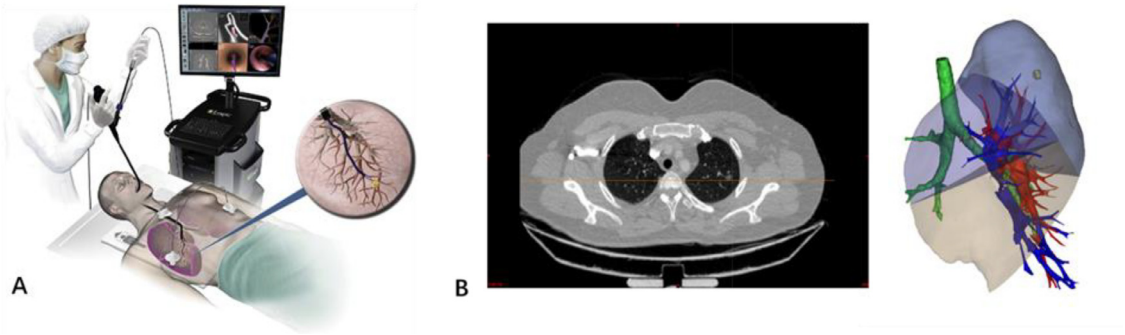

Fig. 5. A: Electromagnetic navigation bronchoscopy: The machine system simulates the three-dimensional reconstruction of the trachea and lungs, and locates the end of the bronchoscope lens to guide the bronchoscope to the target area. (Copyright Elsevier and Copyright Clearance Center).; B: Lung CT shows a ground glass nodule in the apicoposterior segment of the upper lobe of the left lung. The localization of pulmonary nodules under three-dimensional reconstruction is beneficial to accurate segmental resection (Draw from author).

Table 5
Localization methods' advantages and disadvantages.

	Advantages	Disadvantages
CT-guided percutaneous:		
Liquid materials injection: methylene blue dye	Highly successful rate	Short localization time
Hook wire placement	Without intraoperative fluoroscopy and radiation exposure	Dislodgement of the hook wire causes positioning failure
Metallic microcoils and fiducial markers	Decrease the patient's discomfort during the wait before surgery	Requires fluoroscopic guidance during the surgery
Contrast media injection: Lipiodol	Long localization time	Be intraoperatively detected by fluoroscopy
Bronchoscope-guided percutaneous:		
Electromagnetic navigation bronchoscopy (ENB)	Reduce post procedure complications such as pneumothorax, pulmonary hemorrhage, and hemoptysis	Complex positioning operation, higher cost
Virtual assisted lung mapping (VAL-MAP)		
CT virtual 3D positioning		
3D printing/ Virtual reality	Under exploration	

tomography (PET), etc. have low detection rates and poor specificity for tumors with a diameter of less than 1 cm. Therefore, there is an urgent need for early screening methods with high sensitivity and strong specificity.

MRI has the advantages of no ionizing radiation, no half-life influence, multi-plane, and multi-directional images, and higher anatomical resolution. However, the spatial resolution of thoracic MRI is insufficient, and it is not good to observe the fine structure of the lung. So, if synthesized a nanoparticle with paramagnetic signal function, can enter the deep layer of solid lung tumor lesions mediated by a magnetic field, so it can increase the MRI image contrast between solid tumors and surrounding tissues, and improve the resolution of MR for small lesions. Therefore, Yuanpei Li et al. [71] developed an actively targeted, nanosized SPIO nano-platform for therapeutic diagnosis to improve MRI sensitivity and tumor ablation efficacy. In this study, they used cetuximab, a high-affinity anti-EGFR monoclonal antibody, to modify the surface of PEGylated SPIO nanoparticles. It not only improves the biocompatibility of the nanoparticles, but also specifically binds to the highly expressed EGFR receptor on the surface of the H460 lung cancer cell line, which increases the accumulation in the tumor site. According to the results, compared with SPIO NPs without cetuximab functionalization, nanoparticles modified with cetuximab have higher tumor penetration ability and higher resolution of MRI images.

CT imaging has the advantages of short examination time, good contrast of hard tissues, and high spatial resolution [72] and has a good complementarity with MRI. Owning to the tissue and ionizing radiation interaction weakens the contrast efficiency of traditional CT agents and poor sensitivity. In addition, CT and MRI are commonly used and important methods for tumor diagnosis and tumor treatment monitoring in clinical practice. So, the construction of MNPs with CT/MRI dual-modality imaging functions has a better clinical and practical prospect. At present, the most used material in the research of MNPs as a CT imaging component is gold. Due to the high atomic number of golds, gold is used as the coating material of IONPs to construct the core-shell structure Fe3O4@Au MNPs, the magnetic core of IONPs is used as the MRI imaging component, and the gold shell is used as the CT imaging component, making MNPs equipped with MRI/ CT dual-modality imaging function [73]. Tseng et al. [74]used multiple gold NPs to bind to the surface of MNPs. In this study, worm-like mesoporous SiO2 NPs were adsorbed very small IONPs to the surface through electrostatic interaction, and then the gold NPs are anchored outside the silicon shell through the borate bond, thereby constructing a nano-drug carrier system with T1W-MRI/CT dual-modal imaging function, and nano-CT contrast agents have been developed to improve sensitivity.

PET is an effective method for diagnosing a variety of human cancers. Nanoparticles of Gd2O3-doped carbon 11 choline (GdCho) are believed to enhance potential contrast in PET/CT imaging, therefore, Huayang Wu et al. [75] evaluated the efficiency of GdCho-lenvatinib (GdCho-Len-PET) nanoparticles contrast agent to diagnosis the patients were doubted of existing lung cancer. Of the 172 patients, GdCho-PET diagnosed 130 with lung cancer, while GdCho-Len-PET with lenvatinib which is increasing the sensitivity can correctly diagnose 152 patients. In addition, GdCho-Len-PET assistant to anti-cancer therapy in 62 lung cancer patients (90.3%), these patients were candidates for radiotherapy, 57 lung cancer patients (91.2%) received adjuvant radiotherapy, in addition, 13 of the 17 patients (76.5%) received comprehensive treatment. Patients with GdCho-Len-PET assistance improved the subsistence rate of patients during the 420-day follow-up. In summary, nanotechnology enhances the function of the contrast agent, improves the diagnostic efficiency of lung cancer patients, has a significant impact on the survival of lung cancer patients, and may become a reliable method for human cancer diagnosis.

5.2. Nanotechnology for surgical imaging

Optical imaging technology is inseparable from our life, especially in the fields of nanomedicine and tumor surgery, the development of optical imaging technology based on IGS has attracted considerable attention. However, in practical clinical applications, optical imaging technology also faces various challenges, such as 1) how to improve infiltration of deep tissue without weakening the high-intensity contrast; 2) how to accurately identify the tumor by increasing the ratio of SBR or T/NT; 3) how able to last long enough time to satisfy the surgeon to complete all surgical operations; 4) how to quickly remove from the body without obvious toxicity. But what pleases us is the nanoplatform-based optical imaging, which enables us to solve the disadvantage of effective optical imaging techniques in clinical applications, thereby increasing the possibility of IGS moving from the laboratory to the clinic.

5.2.1. Fluorescence imaging

Near-infrared (NIR) fluorescence-guided surgery is an area of development in precision medicine for the treatment of cancer. In terms of tissue penetration, near-infrared light is more advantageous than visible light, due to the less scattering and tissue absorption, Since the FDA approved ICG and fluorescein sodium as fluorescent probes, FGS has been successfully used clinically. Huadong Li et al. [76] used 5-aminolevulinic acid (5-ALA) to create NIRF image-guided surgery system, and discovered that the 5-ALA precursor in the hemoglobin synthesis pathway causes the accumulation of fluorescent porphyrin in various epithelial cells and cancer tissues which can produce better tumor visualization. Robert M Hoffman et al. [77] first transfected a gene expressing red fluorescent protein (RFP) into H460 and A549 cell lines. Then they injected adenovirus OBP-401 containing telomerase-dependent green fluorescent protein (GFP) under fluorescence guidance to a mouse orthotopic lung cancer model. GFP and lung RFP are used to express precisely co-localized lung tumor virus markers. Three days after the injection of OBP-401, the mice were subjected to fluorescence-guided surgery (FGS). According to the fluorescence intensity, lung tumors are selectively and brightly labeled, which is conducive to the complete removal of lung tumors by FGS.

Traditional near-infrared fluorescent reagents have disadvantages such as low sensitivity and specificity to tumors, insufficient light stability, and insufficient tissue penetration depth. To this end, Jingyun Shi et al. [78] constructed a dual-targeting lanthanide-doped near-infrared-visible upconversion nanoprobe for fluorescence imaging of lung cancer. The nanoprobe (UCNP@P-RGD-NGR) is composed of polydopamine-coated NaYF4:Yb/Tm@NaYF4 upconversion nanoparticles (UCNP) coupled with dual targeting peptide RGD10-NGR9, which is designed for targeting integrin $\alpha v\beta 3/\alpha v\beta 5$ receptor and aminopeptidase N receptor are highly expressed on the tumor cell membrane. Through competitive cell binding tests and ICP-MS, it was found that UCNP@P-RGD-NGR can specifically target A549 lung cancer cells (Fig. 6A). The imaging studies of transplanted tumors in BALB/c nude mice show that UCNP@P-RGD-NGR can enhance the up-conversion blue-violet luminescence, so it can locate the tumor location from normal tissues, which provides a huge opportunity for further surgical navigation, it highlights the huge potential for clinical transformation (Fig. 6B). Coincidentally, the NaYF4:Yb,Er,Eu@NaYF4:Nd (NYF:Eu NPs) synthesized by Lu Ruichan and others [79] has multi-modal optics with down-conversion fluorescence in the visible light region, up-conversion luminescence in the visible light region, and near-infrared two-zone NIR II luminescence imaging characteristics, the near-infrared fluorescence emitted by this nanoparticle penetrates deeper and the scattered light is lower (Fig. 6C). When NYF:Eu NPs probes are combined with antibodies against the mined positive hub genes (such as TOP2A and CCNB2), the *in vitro* and in vivo experiments on lung cancer show well-targeted imaging (Fig. 6D). Compared with other cancer cells (such as mouse-derived 4T1) and normal cells, the designed nanoprobe can develop well in human lung cancer cell A549 lesions; and can be used for visualized surgical navigation of lung tumors *in situ*. Those strategies of combining antibodies and optical probes provide an optical imaging method for precision medicine.

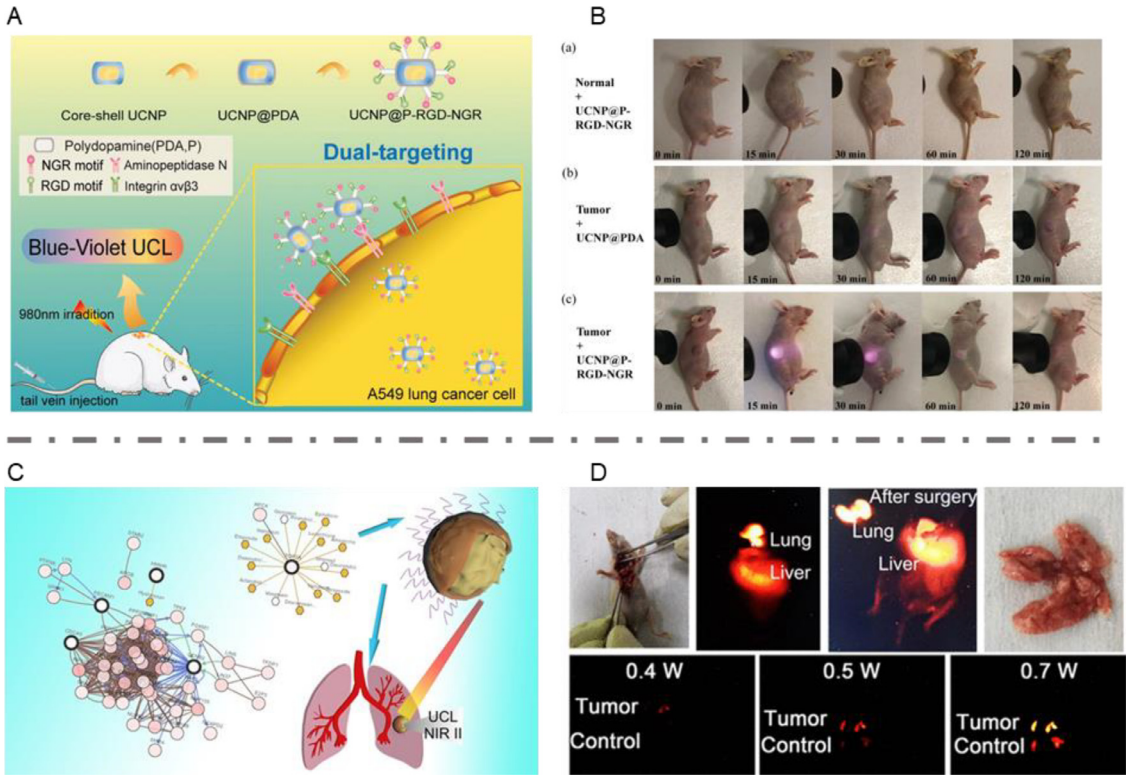

Fig. 6. A: Schematic diagram of the in vivo imaging study of UCNP@P-RGD-NGR and its biological function. It can specifically accumulate in the tumor site and show strong fluorescence. B: *In vivo* imaging of the UCL (Copyright © John Wiley and Sons and Copyright Clearance Center); C: Schematic illustration of multimodal optical imaging of NYF:Eu NPs for down-conversion and up-conversion luminescence in the visible region and luminescence in the near-infrared II region; D: *In situ* imaging and surgery guiding (Copyright © 2021 American Chemical Society).

If the sensitivity can be further improved, it will be expected to be used for early diagnosis and intraoperative navigation.

5.2.2. Photoacoustic imaging (PAI)

As an emerging imaging technique, PAI has been widely used in the imaging of various organs and tissues including tumors. PAI combines the advantages of other imaging modalities, such as the tissue selectivity of pure optical tissue imaging and the tissue depth penetration capability of pure ultrasound tissue imaging. PAI's unique signal collection mode, that is, when the laser is irradiated into biological tissue, is converted into an ultrasonic signal in the light absorption domain of the tissue, so it can provide an advantage that other imaging methods cannot provide – a high-contrast tissue 3D effect, which enables PAIs are increasingly common in clinical applications.

The most widely studied PAI probes can be composed of inorganic and organic materials, as well as probes prepared from activated nanomaterials. In addition, due to the highest extinction coefficient so that gold NPs are widely used in PAI. The function of AuNRs molecules targeting specific binding sites (such as EGFR) has been increasingly valued in biomedicine applications. To observe a significant PA or PPTT effect, many AuNRs need to be in the tumor area. However, only relying on the EPR effect to accumulate large amounts of AuNRs to the tumor site is inefficient. If the targeting ligand is known, the AuNRs can be functionalized with monoclonal antibodies, so that AuNR can accumulate in a large amount to a specific location. As we all know, for lung cancer, EGFR is a positive ligand, therefore, it has become a common method for molecular targeting of multiple imaging technologies. James R. McLaughlan et al. [80] functionalized gold nanorods with anti-EGFR antibodies. The unfunctionalized and functionalized gold nanorods were incubated with lung cancer cells (A549) together and subjected to photothermal treatment. The results showed that after irradiated the pulse wave laser, the cell viability of the targeted nanoparticle group was significantly reduced (93% ± 13%) compared with the unmodified group. Functionalized gold nanoparticles specifically bind to cell receptors, which can improve cell uptake and overall therapeutic effect, which proves the possible application of minimally invasive treatment of lung cancer (Fig. 7A and B).

Semiconducting polymer NPs (SPNs) are also widely used in the preparation of PAI probes. PAI devices composed of SPNs can be used for vascular visualization, LN and tumor detection, guidance for cancer treatment, etc. Compared with inorganic probes, SPNs have better biocompatibility and biodegradability. Chun-Sing Lee et al. [81] prepared and developed electron donor-acceptor conjugated nanoparticles (PPor-PEG NPs) based on semiconducting polymers with good biocompatibility. In this nanosystem, PPor-PEG NPs perform photothermal therapy by trapping units with photothermal effect and then converting light energy into heat energy, and the donor-acceptor facilitates electron transfer and fluorescence quenching, increasing the photothermal conversion efficiency to 62.3%, the highest value among similar nanoparticles that have been reported so far. In addition, the results of the *in vitro* and *in vivo* A549 model showed that PPor-PEG NPs could inhibit tumor growth by 100%. The effect of PPor-PEG NPs demonstrating its excellent photothermal therapy effect. which is the first exploration of polymer applications. The results show that the therapeutic diagnostic agents developed based on polymers can provide an effective solution for the diversity of clinical applications.

5.2.3. Raman imaging

Raman spectroscopy was first discovered in 1928 by Indian physicist Raman et al. [81]. It is a spectroscopy method used to study molecular vibration, which can realize fingerprint recognition of molecular chemical substances, thereby realizing biomolecules' non-destructive testing. Cancer development with various changes, such as nuclear-to-plasma ratio increase, chromatin disorder, etc., Raman spectroscopy with a

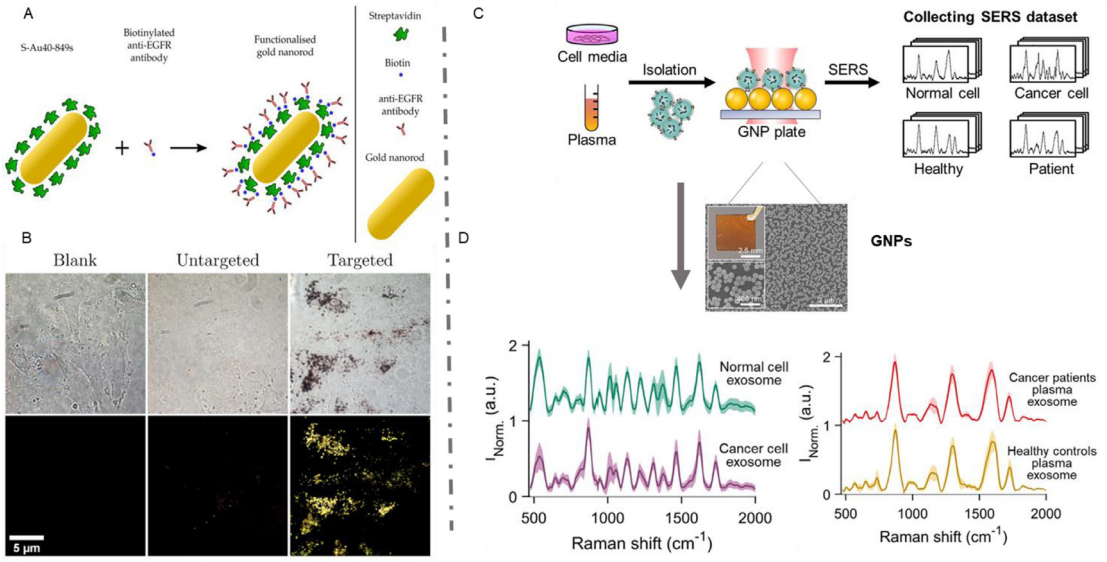

Fig. 7. A: the structure of the biotinylated anti-EGFR antibodies affinity to the AuNR which streptavidin proteins that are already conjugated to the streptavidin proteins; B: 24 h latter, targeted S-Au40-849s can specifically bind to the lung cancer cells (Copyright © 2020 by the authors); C: Schematic illustration of deep learning-based circulating exosome analysis for lung cancer diagnosis; D: Average exosomes SERS signals from cell media supernatant-derived (left) and human plasma-derived (right) (Copyright © 2020 American Chemical Society).

highly sensitive that is suitable for detecting those small molecular level changes, by comparing cancer tissue and the Raman spectrum of normal tissues can be found to reflect the characteristic spectrum of tissue lesion information. Therefore, Raman spectroscopy technology may realize early diagnosis of cancer and guide early treatment.

Early-stage lung cancer has no obvious clinical manifestations. Most patients have already reached the advanced stage when lung cancer is discovered. They miss the best treatment opportunity and have a poor prognosis. For patients with stage I non-small cell lung cancer combined with early interventional therapy, the 5-year overall survival (OS) rate has increased to 73.5%-77.9%, and the 5-year disease-free survival (DFS) rate can be achieved 65.5% -72.7% [82]. Therefore, it is important to reduce the mortality of lung cancer by improving early diagnosis methods. McGregor et al. [83] developed a fast-real-time endoscopic Raman spectroscopy detection system and an endoscopic Raman catheter dedicated to lung detection, which can shorten the detection time to less than 1 s. The study detected 280 tissues in 80 patients (including 72 cases of highly atypical or malignant diseased tissues and 208 cases of benign or normal tissues). The results show that this technique has high susceptible and distinctive for the detection of highly atypical degeneration and malignant lesions, which are 90% and 65% higher, respectively, and the detection is fast and accurate. Weng et al. [84] developed a new technique with automatic identification and diagnosis of lung cancer based on coherent anti-Stokes-Raman scattering techniques combined with deep learning algorithms. This technology can distinguish between normal tissue, small cell lung cancer, adenocarcinoma, and squamous cell carcinoma lung tissue with an accuracy of 89.9%. Therefore, establishing a sample library of different tumor-related markers, capturing and detecting related indicators through liquid biopsy, and conducting early diagnosis of cancer through comparative analysis is a promising technology for clinical application.

In recent years, exosomes have become a hot field in the field of tumor therapy. As one of the tumor-related biomarkers, exosomes have many characteristics, such as carrying genetic and molecular information from their cell of origin. In particular, exosomes from lung cancer tissues with EGFR, CD91, and various microRNAs which are tumor-related biomarkers, and thus can provide useful information for diagnosis. Based on this, we can use roman imaging to detect and differentiate exosomes for disease diagnosis. Yeonho Choi et al. [85] developed early-stage lung cancer diagnosis SERS spectroscopy nanoplatform based on human plasma-derived exosomes. First, they isolated and collected exosomes from cell culture supernatants and human plasma samples, and then incubated them with gold nanoparticle (GNP)-coated plates to gather and enlarge their SERS signals, so finally they successfully established the human plasma exosome signal library consist of healthy and lung cancer patients, which is beneficial for predicting the existence and progression of lung cancer by different Raman signal (Fig. 7 C and D).

5.2.4. *Multi-mode imaging*

The above-mentioned intraoperative imaging methods showed great potential for IGS, but still with some disadvantages [86]. For example, optical fluorescence imaging has high sensitivity and high surface resolution, but optical imaging has low tissue penetration and limited photobleaching. In contrast, PAI has deep penetration, but also has high spatial resolution and can provide 3D images. So, single imaging has shortcomings, and it is difficult to guide the realization of precise photothermal therapy, but the combination of different imaging methods can theoretically achieve complementary advantages with a broader function. Therefore, multi-mode collaborative imaging can give full play to the advantages of various imaging methods.

In response to the above problems, Kuo Chu Hwang et al. [87]designed a theranostic nanomedicine based on multifunctional plasmonic CuO/Cu_2O TNCs, whose surface was partially modified with monoclonal anti-EGFR, which can be specifically targeted Lung cancer cells. In addition, CuO/Cu_2O TNCs exhibit outstanding imaging characteristics with a triple modal, after the use of NIR-I, -II, and -III photoactivated nanomedicines, it can be used for deep diagnosis of lung cancer (MRI/PAI/NIR-II fluorescence imaging), and more importantly, the stimulation of NIR-III PPTT at 1550 nm wavelength also has a therapeutic effect, which can enhance the overall tumor clearing efficiency (Fig. 8A-C). Yuan Zhen et al. [88] successfully synthesized and constructed a new temperature-sensitive tumor-targeted nano-diagnosis and treatment platform UCILA, which incorporated upconversion nanoparticles (UCNPs) and NIR-II organic dye IR-1048 into nucleic acids Aptamer AS1411 modified nanoliposomes (UCILA) to enhance the diagnosis and treatment of non-small cell lung cancer (Fig. 8D). And to study whether it is possible to intuitively obtain com-

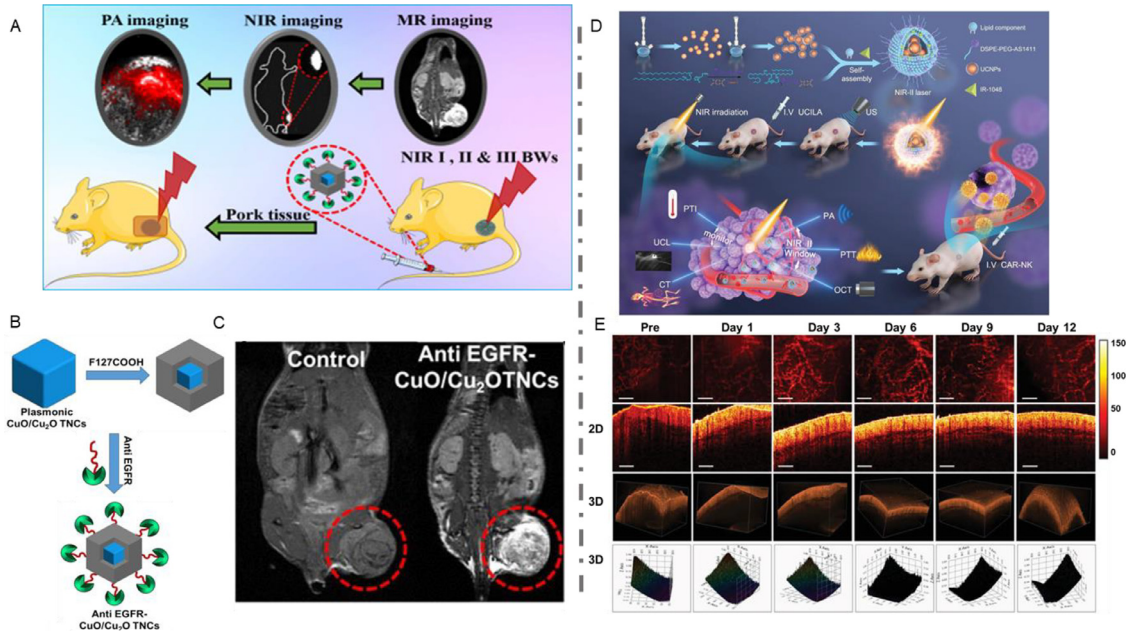

Fig. 8. A: Scheme of the CuO/Cu2O nanocubes, this system with the capable of PAI/MR/NIRF imaging; B: preparing the process of CuO/Cu2O TNCs nanocubes, C: *In vivo* MR imaging function. (Copyright © 2021 American Chemical Society); D: Schematic diagram of the NIR-II five-modality imaging-guided tumor-targeted precision photothermal therapy immunotherapy on the UCILA nanoplatform; E: *In vivo* multiple imaging, and all scale bars of the images range are 4 × 4 mm^2 (Copyright © John Wiley and Sons and Copyright Clearance Center).

prehensive structural and functional information on NSCLC through multimodal imaging while performing tumor photothermal therapy and immunotherapy, the team explored the use of a self-made photoacoustic imaging system, and UCL and other modal imaging methods to monitor the changes and efficacy of tumor microenvironment during the whole process of tumor NIR-II photothermal therapy and CAR-NK immunotherapy (Fig. 8E).

6. Nanotechnology for surgery-assisted synergistic therapy

For most solid tumors, most therapeutic methods think that complete surgical resection can achieve a complete cure, which is extremely difficult in actual clinical situations, also the main reason for postoperative recurrence or metastasis is that surgery can not completely remove all the tumors. Adjuvant therapy is usually implemented before or after surgery to eliminate MRD and improve the outcome of surgery. Broadly speaking, the surgical process of tumors includes two parts, one is the macroscopic surgical resection, and another is microscopic ablation under the assistance of photodynamic therapy (PDT) and photothermal therapy (PTT). Oxygen, light, and photosensitizer are the three key factors for PDT. When photosensitizer is accumulated in the tumor site, then using the laser generates reactive oxygen species (ROS), which is cytotoxic. For PTT, mediated tumor killing is based on the photothermal effect (PTA). When the photothermal transfer agent accumulates in the tumor, the photothermal transfer agent then converts the absorbed light energy into heat, resulting in a microscopic temperature increase that kills tumor cells. So, after surgery, giving emerging ablation treatments can achieve a synergy effect. In addition, photosensitizers and photothermal materials also can provide optical signals. In recent years, the development of multifunctional nano-platforms in combination therapy guided by imaging has attracted more and more attention.

Jonathan F Lovell et al. [89] provided bronchoscopy PDT to some patients who could not undergo surgery due to comorbidities. They designed multimodal "porphyrin" nanoparticle-porphyrin-lipid conjugates with a size of about 100 nm. Porphyrins with high permeability and retention effect that preferentially accumulates in many solid tumors. And also, porphyrin can efficiently convert light energy into heat energy. So, Porphyrin-mediated PTT can largely kill subcutaneous tumors in mice without recurrence.

By taking advantage of the pro-tumor and osmotic properties of mesenchymal stem cells (MSC), biomimetic delivery based on mesenchymal stem cells (MSC) has been actively explored for drug accumulation and penetration into tumors. In this work, Xiaoyi Sun et al. [90] used MSCs as a carry to load Chlorin e6 (Ce6)-conjugated polydopamine nanoparticles (PDA-Ce6). Depending on the properties of MSCs, this nanoparticle can target and penetrate tumors, and then within 72 h, 60% of the payload will be exocytosed. The released PDA-Ce6 NPs can further penetrate the tumor. In a melanoma metastasis of lung cancer mouse model, after MSC-PDA-Ce6 accumulated into the lungs, then using near-infrared radiation to induce PDT and PTT sequentially to trigger selectively toxicity in tumors. Thermosensitive nanomaterials use the inherent or induced high temperature in the tumor cell environment to promote the ablation of tumor cells. Zhiyong Qian et al. [91] combined hollow mesoporous silica nanoparticles (HMSNs) with thermosensitive polymer to prepare a novel injectable hydrogel. At room temperature, the hydrogel solution exists in an injectable, flowing form, but crosslinks with each other at physiological temperatures, transforming the gel mode. The *in vivo* results demonstrated that the gel has a long intratumoral and peritumoral drug retention time, which is beneficial for the in-situ treatment of NSCLC.

7. Conclusion and future prospective

Full resection has the potential to optimally treat cancer and is the first choice for most surgical patients. The emergence of new surgical equipment has brought infinite possibilities for complete resection; more and more precise surgical plans have improved the survival of patients. For instance, vascular replacement, carinal reconstruction, etc. Future developments in pulmonary surgery will continue to be keenly focused on minimizing patient harm, such as the recent proposal of “tubeless surgery”, as well as the continued integration of new technologies into existing thoracoscopic techniques, such as electromagnetic navigation, 3D reconstruction, application of nanotechnology, etc., to achieve complete resection at more than just the visual level.

However, the tumor boundary and microscopic residual lesions cannot be determined only by the doctor's naked eye, so complete resection is a good wish. We have to admit that it is difficult to achieve 100% complete resection by relying only on existing technologies and equipment that can hardly provide real-time surgical imaging. In clinical applications, molecular imaging can expose as many surgical targets as possible, but for obstacles such as thick subcutaneous fat and body cavity septa, the tissue penetration of optical imaging contrast agents is limited. But with the development of nanotechnology and materials science have brought new strategies for surgical treatment, through real-time IGS and surgery-based synergistic anti-cancer strategies, which can provide patients with a full range of accurate testing during the preoperative, intraoperative, and postoperative. We can develop novel contrast agents to enhance tissue penetration for surgical imaging. And the nano-sized carrier, which can flexibly modify specific targeting ligands, can accumulate in large quantities at the disease site after injection, and penetrate to the edge of the tumor tissue to visualize areas that cannot be recognized by the naked eye.

Nanotechnology combined with molecular imaging with high resolution, specificity, and sensitivity brings potential solutions for precise surgery and relatively complete tumor elimination. Although most novel nanomaterials based on IGS or synergistic surgery have failed to achieve clinical translation due to potential tissue safety issues, for example, off-target effects, we need to be concerned that nanosystems in practical applications. However, the results of preclinical research show that it has a considerable therapeutic effect and great potential. It is hoped that researchers can overcome the obstacles in the clinical application of nanotechnology as soon as possible so that it can benefit more patients.

Declaration of Competing Interests

The authors declare no competing interest.

Acknowledgements

This study was supported by Application Research Center of 3D simulation engineering technology for diagnosis and treatment of chest diseases Project No.: 20130604050tc, and we also appreciated that the Academy of Finland (InFLAMES Flagship Grant No. 337531), research Fellow (Grant No. 328933), project (347897), solutions for Health Profile (336355), the Finland China Food and Health International Pilot Project funded by the Finnish Ministry of Education and Culture, and China Scholarship Council support this work.

References

[1] H. Sung, J. Ferlay, R.L. Siegel, M. Laversanne, I. Soerjomataram, A. Jemal, F. Bray, Global Cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA Cancer J. Clin. 71 (2021) 209–249.
[2] H. Qiu, S. Cao, R. Xu, Cancer incidence, mortality, and burden in China: a time-trend analysis and comparison with the United States and United Kingdom based on the global epidemiological data released in 2020, Cancer Commun. (London, England) (2021).
[3] S. Park, I.K. Park, E.R. Kim, Y. Hwang, H.J. Lee, C.H. Kang, Y.T. Kim, Current trends of lung cancer surgery and demographic and social factors related to changes in the trends of lung cancer surgery: an analysis of the national database from 2010 to 2014, Cancer Res. Treat. 49 (2017) 330–337.
[4] J.A. Howington, M.G. Blum, A.C. Chang, A.A. Balekian, S.C. Murthy, Treatment of stage I and II non-small cell lung cancer: diagnosis and management of lung cancer„ in: Chest, 143, 2013, pp. e278S–e313S.
[5] D.J. Sher, M.J. Fidler, M.J. Liptay, M. Koshy, Comparative effectiveness of neoadjuvant chemoradiotherapy versus chemotherapy alone followed by surgery for patients with stage IIIA non-small cell lung cancer, Lung Cancer (Amsterdam, Netherlands) 88 (2015) 267–274.
[6] E.A. Graham, J.J. Singer, Landmark article Oct 28, 1933. Successful removal of an entire lung for carcinoma of the bronchus. By Evarts A. Graham and J. J. Singer, JAMA 251 (1984) 257–260.
[7] G. Roviaro, C. Rebuffat, F. Varoli, C. Vergani, C. Mariani, M. Maciocco, Videoendoscopic pulmonary lobectomy for cancer, Surg. Laparosc. Endosc. 2 (1992) 244–247.
[8] J. He, History and current status of mini-invasive thoracic surgery, J. Thorac. Dis. 3 (2011) 115–121.
[9] C.P. Thomas, Conservative resection of the bronchial tree, J. R. Coll. Surg. Edinb. 1 (1956) 169–186.
[10] M.B. Shimkin, R.R. Connelly, S.C. Marcus, S.J. Cutler, Pneumonectomy and lobectomy in bronchogenic carcinoma. A comparison of end results of the Overholt an d Ochsner clinics, J. Thorac. Cardiovasc. Surg. 44 (1962) 503–519.
[11] R.J. Jensik, L.P. Faber, F.J. Milloy, D.O. Monson, Segmental resection for lung cancer. A fifteen-year experience, J. Thorac. Cardiovasc. Surg. 66 (1973) 563–572.
[12] R.P. Petersen, D. Pham, E.M. Toloza, W.R. Burfeind, D.H. Harpole, S.I. Hanish, T.A. D'Amico, Thoracoscopic lobectomy: a safe and effective strategy for patients receiving induction therapy for n on-small cell lung cancer, Ann. Thorac. Surg. 82 (2006) 214–218 discussion 219.
[13] S.J. Swanson, J.E. Herndon, T.A. D'Amico, T.L. Demmy, R.J. McKenna, M.R. Green, D.J. Sugarbaker, Video-assisted thoracic surgery lobectomy: report of CALGB 39802–a prospective, multi-institution fe asibility study, J. Clin. Oncol. 25 (2007) 4993–4997.
[14] D. Gonzalez, M. Paradela, J. Garcia, M. Dela Torre, Single-port video-assisted thoracoscopic lobectomy, Interact Cardiovasc Thorac Surg 12 (2011) 514–515.
[15] J.S. Chen, Y.J. Cheng, M.H. Hung, Y.D. Tseng, K.C. Chen, Y.C. Lee, Nonintubated thoracoscopic lobectomy for lung cancer, Ann. Surg. 254 (2011) 1038–1043.
[16] C. Cao, C. Manganas, S.C. Ang, T.D. Yan, A systematic review and meta-analysis on pulmonary resections by robotic video-assisted thoracic surgery, Ann Cardiothorac Surg 1 (2012) 3–10.
[17] M. Li, The world's first radical resection for lung cancer using glasses-free 3D thoracoscope was completed in Guangzhou, J. Thorac. Dis. 7 (2015) E384–E385.
[18] A. Abbas, S. Kadakia, V. Ambur, K. Muro, L. Kaiser, Intraoperative electromagnetic navigational bronchoscopic localization of small, deep, or subsolid pu lmonary nodules, J. Thorac. Cardiovasc. Surg. 153 (2017) 1581–1590.
[19] B. Fisher, S. Anderson, J. Bryant, R.G. Margolese, M. Deutsch, E.R. Fisher, J.H. Jeong, N. Wolmark, Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer, N. Engl. J. Med. 347 (2002) 1233–1241.
[20] C. Wang, W. Fan, Z. Zhang, Y. Wen, L. Xiong, X. Chen, Advanced nanotechnology leading the way to multimodal imaging-guided precision surgical therapy, Adv. Mater. 31 (2019) e1904329.
[21] Y. Dang, J. Guan, Nanoparticle-based drug delivery systems for cancer therapy, Smart Mater. Med. 1 (2020) 10–19.
[22] Z. Guo, H. Liu, W. Dai, Y. Lei, Responsive principles and applications of smart materials in biosensing, Smart Mater. Med. 1 (2020) 54–65.
[23] J. Pellico, C.M. Ellis, J.J. Davis, Nanoparticle-based paramagnetic contrast agents for magnetic resonance imaging, Contrast Media Mol. Imaging (2019) 1845637 2019.
[24] N. Lan, M. Hao, C.M. Niu, H. Cui, Y. Wang, T. Zhang, P. Fang, C.H. Chou, Next-Generation Prosthetic Hand: from Biomimetic to Biorealistic, Research (Wash D C), 2021 (2021) 4675326.
[25] F.C. Detterbeck, The eighth edition TNM stage classification for lung cancer: what does it mean on main street? J. Thorac. Cardiovasc. Surg. 155 (2018) 356–359.
[26] A.P. Naef, [Development of thoracic surgery from 1880 to the present], Rev. Med. Suisse Romande 107 (1987) 949–957.
[27] E.A. Rendina, T. De Giacomo, F. Venuta, A.M. Ciccone, G.F. Coloni, Lung conservation techniques: bronchial sleeve resection and reconstruction of the pulmonary artery, Semin. Surg. Oncol. 18 (2000) 165–172.
[28] L. Spaggiari, F. Leo, G. Veronesi, P. Solli, D. Galetta, B. Tatani, F. Petrella, D. Radice, Superior vena cava resection for lung and mediastinal malignancies: a single-center experience with 7 0 cases, Ann. Thorac. Surg. 83 (2007) 223–229 discussion 229-230.
[29] K. Yokoi, T. Taniguchi, N. Usami, K. Kawaguchi, T. Fukui, F. Ishiguro, Surgical management of locally advanced lung cancer, Gen. Thorac. Cardiovasc. Surg. 62 (2014) 522–530.
[30] T.D. Yan, D. Black, P.G. Bannon, B.C. McCaughan, Systematic review and meta-analysis of randomized and nonrandomized trials on safety and efficacy of video-assisted thoracic surgery lobectomy for early-stage non-small-cell lung cancer, J. Clin. Oncol. 27 (2009) 2553–2562.
[31] C. Cao, C. Manganas, S.C. Ang, S. Peeceeyen, T.D. Yan, Video-assisted thoracic surgery versus open thoracotomy for non-small cell lung cancer: a meta-analys is of propensity score-matched patients, Interact. Cardiovasc. Thorac. Surg. 16 (2013) 244–249.
[32] A.D. Sihoe, The evolution of minimally invasive thoracic surgery: implications for the practice of uniportal thor acoscopic surgery, J. Thorac. Dis. 6 (2014) S604–S617.
[33] H.K. Kim, H.K. Sung, H.J. Lee, Y.H. Choi, The feasibility of a two-incision video-assisted thoracoscopic lobectomy, J. Cardiothorac. Surg. 8 (2013) 88.
[34] A.D.L. Sihoe, B. Han, T.Y. Yang, C. Pan, G. Jiang, V.W.T. Fang, The advent of ultra-high volume thoracic surgical centers in Shanghai, World J. Surg. 41 (2017) 2758–2768.
[35] L.A. Hernandez-Arenas, L. Lin, Y. Yang, M. Liu, W. Guido, D. Gonzalez-Rivas, G. Jiang, L. Jiang, Initial experience in uniportal subxiphoid video-assisted thoracoscopic surgery for major lung resect ions, Eur. J. Cardiothorac. Surg. 50 (2016) 1060–1066.
[36] A.D.L. Sihoe, Uniportal lung cancer surgery: state of the evidence, Ann. Thorac. Surg. 107 (2019) 962–972.
[37] G. Rocco, One-port (uniportal) video-assisted thoracic surgical resections–a clear advance, J. Thorac. Cardiovasc. Surg. 144 (2012) S27–S31.
[38] L. Bulgarelli Maqueda, A. Garcia-Perez, A. Minasyan, D. Gonzalez-Rivas, Uniportal VATS for non-small cell lung cancer, Gen. Thorac. Cardiovasc. Surg. 68 (2020) 707–715.
[39] C.W. Kennedy, T. Hu, J.P. Desai, A.S. Wechsler, J.Y. Kresh, Cardiovas. Eng. 2 (2002) 15–22.
[40] B.J. Park, R.M. Flores, V.W. Rusch, Robotic assistance for video-assisted thoracic surgical lobectomy: technique and initial results, J. Thorac. Cardiovasc. Surg. 131 (2006) 54–59.

[41] A.E. Abbas, Robotic portal lobectomy, surgery through a virtual thoracotomy, J. Thorac. Dis. 9 (2017) 2871–2875.
[42] A.E. Abbas, Surgical management of lung cancer: history, evolution, and modern advances, Curr. Oncol. Rep. 20 (2018) 98.
[43] J. Gothard, Lung injury after thoracic surgery and one-lung ventilation, Curr. Opin. Anaesthesiol. 19 (2006) 5–10.
[44] T.C. Mineo, E. Pompeo, D. Mineo, F. Tacconi, M. Marino, A.F. Sabato, Awake non-resectional lung volume reduction surgery, Ann. Surg. 243 (2006) 131–136.
[45] Y.D. Tseng, Y.J. Cheng, M.H. Hung, K.C. Chen, J.S. Chen, Nonintubated needlescopic video-assisted thoracic surgery for management of peripheral lung nodules, Ann. Thorac. Surg. 93 (2012) 1049–1054.
[46] C.Y. Wu, J.S. Chen, Y.S. Lin, T.M. Tsai, M.H. Hung, K.C. Chan, Y.J. Cheng, Feasibility and safety of nonintubated thoracoscopic lobectomy for geriatric lung cancer patients, Ann. Thorac. Surg. 95 (2013) 405–411.
[47] M.H. Hung, H.H. Hsu, K.C. Chen, K.C. Chan, Y.J. Cheng, J.S. Chen, Nonintubated thoracoscopic anatomical segmentectomy for lung tumors, Ann. Thorac. Surg. 96 (2013) 1209–1215.
[48] F. Cui, J. Liu, S. Li, W. Yin, X. Xin, W. Shao, J. He, Tubeless video-assisted thoracoscopic surgery (VATS) under non-intubated, intravenous anesthesia with spontaneous ventilation and no placement of chest tube postoperatively, J. Thorac. Dis. 8 (2016) 2226–2232.
[49] M.W. Lin, J.S. Chen, Image-guided techniques for localizing pulmonary nodules in thoracoscopic surgery, J. Thorac. Dis. 8 (2016) S749–s755.
[50] R.E. Vandoni, J.F. Cuttat, S. Wicky, M. Suter, CT-guided methylene-blue labelling before thoracoscopic resection of pulmonary nodules, Eur. J. Cardiothorac. Surg. 14 (1998) 265–270.
[51] B. Kidane, K. Yasufuku, Advances in image-guided thoracic surgery, Thorac. Surg. Clin. 26 (2016) 129–138.
[52] Y.R. Chen, K.M. Yeow, J.Y. Lee, I.H. Su, S.Y. Chu, C.H. Lee, Y.C. Cheung, H.P. Liu, CT-guided hook wire localization of subpleural lung lesions for video-assisted thoracoscopic surgery (VATS), J. Formos. Med. Assoc. 106 (2007) 911–918.
[53] S.W. Moon, Y.P. Wang, K.H. Jo, M.S. Kwack, S.W. Kim, O.K. Kwon, H.S. Jang, Fluoroscopy-aided thoracoscopic resection of pulmonary nodule localized with contrast media, Ann. Thorac. Surg. 68 (1999) 1815–1820.
[54] K. Luo, Y. Lin, X. Lin, X. Yu, J. Wen, K. Xi, P. Lin, L. Zhang, Localization of peripheral pulmonary lesions to aid surgical resection: a novel approach for electrom agnetic navigation bronchoscopic dye marking, Eur. J. Cardiothorac. Surg. 52 (2017) 516–521.
[55] M. Sato, M. Omasa, F. Chen, T. Sato, M. Sonobe, T. Bando, H. Date, Use of virtual assisted lung mapping (VAL-MAP), a bronchoscopic multispot dye-marking technique using virtual images, for precise navigation of thoracoscopic sublobar lung resection, J. Thorac. Cardiovasc. Surg. 147 (2014) 1813–1819.
[56] L. Zhang, M. Li, Z. Li, X. Kedeer, L. Wang, Z. Fan, C. Chen, Three-dimensional printing of navigational template in localization of pulmonary nodule: a pilot study, J. Thorac. Cardiovasc. Surg. 154 (2017) 2113–2119 e2117.
[57] R.J. Ginsberg, L.V. Rubinstein, Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. Lung Cancer Study Group, Ann. Thorac. Surg. 60 (1995) 615–622 discussion 622-613.
[58] J.P. Wisnivesky, C.I. Henschke, S. Swanson, D.F. Yankelevitz, J. Zulueta, S. Marcus, E.A. Halm, Limited resection for the treatment of patients with stage IA lung cancer, Ann. Surg. 251 (2010) 550–554.
[59] K. Nakamura, H. Saji, R. Nakajima, M. Okada, H. Asamura, T. Shibata, S. Nakamura, H. Tada, M. Tsuboi, A phase III randomized trial of lobectomy versus limited resection for small-sized peripheral non-sma ll cell lung cancer (JCOG0802/WJOG4607L), Jpn. J. Clin. Oncol. 40 (2010) 271–274.
[60] H. Saji, M. Okada, M. Tsuboi, R. Nakajima, K. Suzuki, K. Aokage, T. Aoki, J. Okami, I. Yoshino, H. Ito, N. Okumura, M. Yamaguchi, N. Ikeda, M. Wakabayashi, K. Nakamura, H. Fukuda, S. Nakamura, T. Mitsudomi, S.I. Watanabe, H. Asamura, G. West Japan Oncology, G. Japan Clinical Oncology, Segmentectomy versus lobectomy in small-sized peripheral non-small-cell lung cancer (JCOG0802/WJOG460 7L): a multicentre, open-label, phase 3, randomised, controlled, non-inferiority trial, Lancet 399 (2022) 1607–1617.
[61] N. Ikeda, A. Yoshimura, M. Hagiwara, S. Akata, H. Saji, Three dimensional computed tomography lung modeling is useful in simulation and navigation of lung ca ncer surgery, Ann. Thorac. Cardiovasc. Surg. 19 (2013) 1–5.
[62] T. Nakada, T. Akiba, T. Inagaki, T. Morikawa, Thoracoscopic anatomical subsegmentectomy of the right S2b + S3 using a 3D printing model with rapid prototyping, Interact. Cardiovasc. Thorac. Surg. 19 (2014) 696–698.
[63] M. Gao, F. Yu, C. Lv, J. Choo, L. Chen, Fluorescent chemical probes for accurate tumor diagnosis and targeting therapy, Chem. Soc. Rev. 46 (2017) 2237–2271.
[64] R.K. Jain, T. Stylianopoulos, Delivering nanomedicine to solid tumors, Nat. Rev. Clin. Oncol. 7 (2010) 653–664.
[65] P. Enck, Q. Aziz, G. Barbara, A.D. Farmer, S. Fukudo, E.A. Mayer, B. Niesler, E.M. Quigley, M. Rajilic-Stojanovic, M. Schemann, J. Schwille-Kiuntke, M. Simren, S. Zipfel, R.C. Spiller, Irritable bowel syndrome, Nat. Rev. Dis. Primers 2 (2016) 16014.
[66] L.E. Ibarra, Development of nanosystems for active tumor targeting in photodynamic therapy, Ther. Deliv. 13 (2022) 71–74.
[67] Z. Deng, G.T. Kalin, D. Shi, V.V. Kalinichenko, Nanoparticle delivery systems with cell-specific targeting for pulmonary diseases, Am. J. Respir. Cell Mol. Biol. 64 (2021) 292–307.
[68] N. Muhamad, T. Plengsuriyakarn, K. Na-Bangchang, Application of active targeting nanoparticle delivery system for chemotherapeutic drugs and traditional/herbal medicines in cancer therapy: a systematic review, Int. J. Nanomed. 13 (2018) 3921–3935.
[69] M. Scaltriti, J. Baselga, The epidermal growth factor receptor pathway: a model for targeted therapy, Clin. Cancer Res. 12 (2006) 5268–5272.
[70] J. Garousi, K.G. Andersson, B. Mitran, M.L. Pichl, S. Stahl, A. Orlova, J. Lofblom, V. Tolmachev, PET imaging of epidermal growth factor receptor expression in tumours using 89Zr-labelled ZEGFR:2377 affibody molecules, Int. J. Oncol. 48 (2016) 1325–1332.
[71] Z. Wang, R. Qiao, N. Tang, Z. Lu, H. Wang, Z. Zhang, X. Xue, Z. Huang, S. Zhang, G. Zhang, Y. Li, Active targeting theranostic iron oxide nanoparticles for MRI and magnetic resonance-guided focused ultrasound ablation of lung cancer, Biomaterials 127 (2017) 25–35.
[72] D. Elkon, J.A. Kim, W.C. Constable, CT scanning and interstitial therapy, J. Comput. Tomogr. 5 (1981) 268–272.
[73] N.V.S. Vallabani, S. Singh, A.S. Karakoti, Magnetic nanoparticles: current trends and future aspects in diagnostics and nanomedicine, Curr. Drug Metab. 20 (2019) 457–472.
[74] H.L. Perry, R.M. Botnar, J. Wilton-Ely, Gold nanomaterials functionalised with gadolinium chelates and their application in multimodal imaging and therapy, Chem. Commun. (Camb.) 56 (2020) 4037–4046.
[75] T. Zhou, D. Hang, Y. Li, J. Zhang, H. Wu, H. Wang, E. Tian, J. Yan, Role of Gd2O3-doped carbon-11-choline-lenvatinib nanoparticles contrast agent PET/CT in the diagnosis of patients with lung cancer, Oncol. Lett. 19 (2020) 1117–1124.
[76] S. Zhao, J. Wu, C. Wang, H. Liu, X. Dong, C. Shi, C. Shi, Y. Liu, L. Teng, D. Han, X. Chen, G. Yang, L. Wang, C. Shen, H. Li, Intraoperative fluorescence-guided resection of high-grade malignant gliomas using 5-aminolevulinic acid-induced porphyrins: a systematic review and meta-analysis of prospective studies, PLoS One 8 (2013) e63682.
[77] S. Yano, Y. Zhang, S. Miwa, H. Kishimoto, Y. Urata, M. Bouvet, S. Kagawa, T. Fujiwara, R.M. Hoffman, Precise navigation surgery of tumours in the lung in mouse models enabled by in situ fluorescence labelling with a killer-reporter adenovirus, BMJ Open Respir. Res. 2 (2015) e000096.
[78] J. Cao, L. Zhang, X. Ding, D. Liu, B. Su, J. Shi, Dual-targeting peptides RGD10-NGR9-conjugated lanthanide Nanoparticle@Polydopamine as upconversion nanoprobes for in vivo imaging of lung cancer, Small Methods 4 (2020) 2000648.
[79] R. Lv, Y. Wang, B. Lin, X. Peng, J. Liu, W.D. Lu, J. Tian, Targeted luminescent probes for precise upconversion/NIR II luminescence diagnosis of lung adenocarcinoma, Anal. Chem. 93 (2021) 4984–4992.
[80] O. Knights, S. Freear, J.R. McLaughlan, Improving plasmonic photothermal therapy of lung cancer cells with Anti-EGFR targeted gold nanorods, Nanomaterials (Basel) (2020) 10.
[81] C.V. Raman, K.S. Krishnan, A new type of secondary radiation (Reprinted from Nature, vol 121, pg 501-502, 1928), Curr. Sci. India 74 (1998) 381 -381.
[82] X. Tian, Y. Zhang, [Research Progress of Raman Spectroscopy in the Diagnosis of Early Lung Cancer], Zhongguo Fei Ai Za Zhi 21 (2018) 560–564.
[83] H.C. McGregor, M.A. Short, A. McWilliams, T. Shaipanich, D.N. Ionescu, J. Zhao, W. Wang, G. Chen, S. Lam, H. Zeng, Real-time endoscopic Raman spectroscopy for in vivo early lung cancer detection, J. Biophoton. 10 (2017) 98–110.
[84] S. Weng, X. Xu, J. Li, S.T.C. Wong, Combining deep learning and coherent anti-Stokes Raman scattering imaging for automated differential diagnosis of lung cancer, J. Biomed. Opt. 22 (2017) 1–10.
[85] H. Shin, S. Oh, S. Hong, M. Kang, D. Kang, Y.G. Ji, B.H. Choi, K.W. Kang, H. Jeong, Y. Park, S. Hong, H.K. Kim, Y. Choi, Early-stage lung cancer diagnosis by deep learning-based spectroscopic analysis of circulating exosomes, ACS Nano 14 (2020) 5435–5444.
[86] D. Zheng, Y. Chen, S. Ai, R. Zhang, Z. Gao, C. Liang, L. Cao, Y. Chen, Z. Hong, Y. Shi, L. Wang, X. Li, Z. Yang, Tandem molecular self-assembly selectively inhibits lung cancer cells by inducing endoplasmic reticulum stress, Res. (Wash D C) (2019) 4803624 2019.
[87] M. Shanmugam, N. Kuthala, R. Vankayala, C.S. Chiang, X. Kong, K.C. Hwang, Multifunctional CuO/Cu2O truncated nanocubes as trimodal image-guided near-infrared-III photothermal agents to combat multi-drug-resistant lung carcinoma, ACS Nano 15 (2021) 14404–14418.
[88] M. Xu, B. Xue, Y. Wang, D. Wang, D. Gao, S. Yang, Q. Zhao, C. Zhou, S. Ruan, Z. Yuan, Temperature-feedback nanoplatform for NIR-II penta-modal imaging-guided synergistic photothermal therapy and CAR-NK immunotherapy of lung cancer, Small 17 (2021) e2101397.
[89] J.F. Lovell, C.S. Jin, E. Huynh, H. Jin, C. Kim, J.L. Rubinstein, W.C. Chan, W. Cao, L.V. Wang, G. Zheng, Porphysome nanovesicles generated by porphyrin bilayers for use as multimodal biophotonic contrast agents, Nat. Mater. 10 (2011) 324–332.
[90] X. Ouyang, X. Wang, H.B. Kraatz, S. Ahmadi, J. Gao, Y. Lv, X. Sun, Y. Huang, A Trojan horse biomimetic delivery strategy using mesenchymal stem cells for PDT/PTT therapy against lung melanoma metastasis, Biomater. Sci. 8 (2020) 1160–1170.
[91] X. Zhou, X. He, K. Shi, L. Yuan, Y. Yang, Q. Liu, Y. Ming, C. Yi, Z. Qian, Injectable thermosensitive hydrogel containing erlotinib-loaded hollow mesoporous silica nanoparticles as a localized drug delivery system for NSCLC therapy, Adv. Sci. (Weinh) 7 (2020) 2001442.