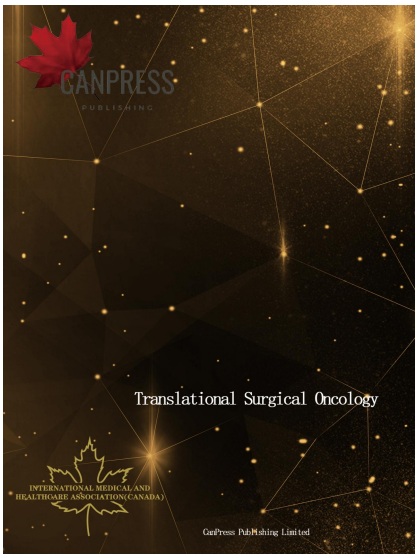
Current status of radical resection of lung cancer combined with coronary artery bypass grafting



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Abstract

With the aging of the population, the incidence of lung cancer combined with coronary heart disease has been increasing yearly, which seriously threatens the life and health of patients. The treatment of lung cancer combined with coronary heart disease is rather difficult. Radical resection of lung cancer (RRLC) combined with coronary artery bypass grafting (CABG) is an effective treatment method. Compared with staged surgery, simultaneous surgery can avoid the delay of lung cancer treatment, the need for a second anesthesia, and patients' fear of reoperation, but it may increase surgical risks and postoperative complications. By examining updated literatures, this review summarizes current status of the application of RRLC combined with CABG for the treatment of lung cancer patients combined with coronary heart disease, so as to provide medical evidence for clinical application of this surgical procedure.

Keywords: coronary artery bypass grafting; coronary heart disease; radical resection of lung cancer; surgery

Introduction

In recent years, the aging process has accelerated in China, and the incidence of malignant tumors and coronary heart disease has been increasing yearly. Coronary heart disease has gradually become an important disease to threaten the life and health of cancer patients. Due to comorbidities with coronary heart disease, such as smoking, environmental pollution, and age, lung cancer combined with severe coronary heart disease occurs in some patients, leading to delayed lung cancer surgery and increased risk of tumor progression and metastasis. The combined incidence of lung cancer and coronary heart disease is on the rise [1]. For patients with early-stage non-small cell lung cancer (NSCLC) (stage I, II, and some stage IIIa) who meet criteria, it is recommended to undergo surgical resection to achieve the purpose of treatment, as N2 lymph node lesions are usually found during surgery in these stage IIIa patients [2]. The 8th edition of the American Joint Committee on Cancer (AJCC) staging system distinguishes between resectable and unresectable Stage IIIa pancreatic cancer primarily based on tumor size (T) and lymph node involvement (N) [3]. However, if NSCLC patients with surgical indications are found to have severe coronary heart disease during initial diagnosis, coronary heart disease can become an obstacle to radical resection of lung cancer (RRLC), and combined with coronary artery bypass grafting (CABG) is often required at this time. The early treatment strategy for this type of patient is staged surgery, i.e., CABG is performed first, and RRLC is performed after the condition stabilizes. However, staged surgery has many problems, such as delaying the timing of lung cancer treatment, requiring patients to undergo two anesthetics, increasing total hospitalization costs and time, and the fear of patients facing reoperation.

Safety and feasibility of RRLC combined with concurrent CABG surgery

Bricker et al. explored the safety and feasibility of RRLC combined with concurrent CABG surgery, and reported two successful cases in 1980 [4]. One case was a 70-year-old male patient diagnosed with central squamous cell carcinoma of the left lung combined with coronary heart disease (complete

occlusion of the right coronary artery and 90% stenosis of the left anterior descending artery). Under general anesthesia and cardiopulmonary bypass (CPB), left anterior descending artery CABG was performed through bilateral anterior lateral incisions of the fourth intercostal space, followed by concurrent radical resection of left lung (left pneumonectomy). The patient recovered well and was discharged 11 days after surgery. He died of tumor recurrence 35 months after surgery. Another case was a 49-year-old male patient diagnosed with right upper lobe lung cancer combined with coronary heart disease (90% stenosis of left anterior descending artery and diagonal branch). Under general anesthesia and CPB, left anterior descending artery and diagonal branch CABG were performed through a median sternotomy incision using the great saphenous vein, followed by concurrent radical resection of right lung (right upper and right middle lobectomy). On the third day after surgery, the patient underwent tracheotomy and mechanical ventilation due to a large amount of bronchial secretions. After receiving oxygen therapy and enhanced anti-infective treatment, the patient improved, and weaning and extubation was performed. He died of tumor recurrence 42 months after surgery. The above two patients successfully underwent RRLC combined with concurrent CABG surgery, survived the perioperative period, recovered well after surgery, and ultimately died of tumor progression, which was considered to be related to the limited anti-tumor treatment options at that time.

Subsequently, several retrospective studies confirmed that RRLC combined with concurrent CABG surgery was safe and feasible [5]. With the development of novel surgical techniques, RRLC combined with concurrent CABG surgery has been continuously improved.

Surgical indications for RRLC combined with concurrent CABG surgery

For patients with locally advanced NSCLC, the goal of radical treatment has often been achieved through pneumonectomy or combined lobectomy. However, pneumonectomy or combined lobectomy can cause significant damage and trauma to lung function, resulting in higher postoperative complications and mortality. If concurrent CABG is performed, postoperative complications and mortality will further increase. Fortunately, various anti-tumor drugs, especially targeted drugs and immune checkpoint inhibitors have been developed recently. Therefore, lung cancer treatment has entered the era of targeted therapy and immunotherapy. For patients with locally advanced and advanced NSCLC, chemotherapy, radiotherapy, targeted drug therapy, and immune checkpoint inhibitor therapy are preferred, and surgery is not the first choice [6]. Therefore, the staging of patients with NSCLC combined with coronary heart disease undergoing simultaneous surgery are mainly concentrated in stages I, II, and partially resectable stage IIIa. However, lung adenocarcinoma mainly characterized by ground-glass nodules develops to invasive cancer at a slower rate, and the chance of metastasis in most patients is relatively low throughout their lifetime [7]. These patients will not experience tumor progression during 1 to 3 months of follow-up, and can choose staged surgery. For patients with a history of myocardial infarction, percutaneous coronary intervention (PCI) failure, or unstable angina, especially those who cannot undergo a second surgery, combined surgery is considered safe, with a good prognosis [8].

The simultaneous surgical treatment strategy has the following problems: (1) dual antiplatelet therapy (DAPT) is required after PCI, and lung surgery can only be performed after at least 1–3 months, which may delay lung cancer treatment and lead to tumor progression [9]; (2) preoperative use of DAPT may increase the risk of pulmonary surgical bleeding and oozing; (3) blood hypercoagulability during radiotherapy and chemotherapy can lead to stent blockage and other issues; (4) during RRLC under general anesthesia, adverse cardiac events occur due to stent reobstruction. Marcucci et al. suggested that balloon dilatation should be preferred over stent placement in preoperative revascularization, and PCI should be performed after the patient has fully recovered from lung cancer surgery [10]. However, balloon dilatation is not effective for some lesions with severe calcification, vascular bent or bifurcation part, and there is a risk of acute vascular occlusion. Therefore, for patients with lung cancer combined with coronary heart disease, the indications for CABG can be appropriately relaxed. When performing staged surgery, CABG should be performed first before RRLC. Although it can achieve ideal treatment results, attention should be paid to shortening the interval between the two surgeries as much as possible, while ensuring that it does not affect the good recovery state after CABG surgery [11]. Nevertheless, staged surgery still faces the problems of postoperative antiplatelet therapy and deferred surgery for CAGB. With the development of minimally invasive medical technology, the perioperative risks of simultaneous surgery have been reduced, and the safety and feasibility have been improved. However, not all patients are suitable for simultaneous surgery, and patients with poor cardiopulmonary function are not suitable for simultaneous surgery.

Surgical sequence of RRLC combined with concurrent CABG surgery

In the era of CPB, most lung cancer patients with coronary heart disease undergo CABG first and then undergo RRLC, mainly to reduce the occurrence of cardiovascular adverse events during surgery. The disadvantage is that performing CABG first requires heparinization, which may lead to increased bleeding and oozing during subsequent lung cancer surgery. In addition, the damage of CPB to the body cannot be ignored. Studies have shown that CPB has inhibitory effects on various components of the immune system, including the

activity of natural killer cells, which is also inhibited by CPB and continues to be inhibited after surgery [12]. These known immune response changes may promote tumor growth and spread. In addition, it may be possible for tumor to spread and metastasize with CPB [13]. The dilemma of CPB has been resolved with the emergence of off-pump coronary artery bypass grafting (OPCABG) technique. With the improvement of OPCABG technique, most CABGs can choose this surgical procedure. OPCABG avoids adverse reactions caused by CPB, reduces heparin dosage, lowers the risk of intraoperative bleeding and oozing, and reduces the occurrence of postoperative complications [14]. Multiple cohort studies have shown that RRLC combined with concurrent OPCABG surgery is safe and feasible for the treatment of patients with lung tumors combined with severe coronary heart disease [15-17]. Our experience is that if CPB is required for surgery, RRLC should be performed first if coronary artery conditions permit. On the one hand, this can reduce bleeding and oozing, and on the other hand, it can minimize the adverse effects of CPB. When using non-CPB, the surgical sequence is relatively flexible and can be chosen according to the specific situation of the patient.

Surgical incision for RRLC combined with concurrent CABG surgery

Early RRLC combined with concurrent CABG surgery mainly adopts a median sternotomy incision and a fourth intercostal anterior lateral incision. Among them, the median sternotomy incision is a commonly used incision in cardiac surgery. The surgical field of CABG is well exposed, but the difficulty to cut the lungs through this incision increases. Especially, the left lower lobectomy of the lung through the median sternotomy incision is considered the most difficult, and lymph node dissection is also difficult, making it difficult to be completely dissected. Insufficient lymph node assessment and incomplete dissection are considered important factors for poor long-term prognosis of patients treated with combination therapy [18]. In order to solve the problem of incomplete exposure of lung cutting by median sternotomy incision, some scholars adopt a median incision for CABG, and then switch positions to perform RRLC with lateral thoracotomy. The advantage of this surgical procedure is that the exposure of the two surgical fields is relatively clear, but the disadvantage is that the trauma is large, and there are many postoperative complications such as wound pain and lung infection. For some patients with coronary artery lesions and lung lesions on the same side, some scholars adopt the method of lateral thoracotomy [19]. Lateral thoracotomy is beneficial for RRLC, but it increases the difficulty of CABG.

With the development of minimally invasive thoracoscopy, most RRLCs can be performed under laparoscopy, changing the traditional mode of lateral thoracotomy for RRLC from three-hole to double-hole to single-hole. The application of minimally invasive thoracoscopy in the treatment of lung cancer combined with coronary heart disease marks an important step towards minimally invasive surgery for RRLC combined with concurrent CABG surgery. The application of thoracoscopy in RRLC combined with concurrent CABG surgery results in a more minimally invasive incision, with better exposure of the surgical field and favorable conditions for lymph node dissection, thus reducing postoperative pain and pulmonary complications.

Notably, minimally invasive small lateral thoracotomy for CABG has become a new surgical procedure [20]. When minimally invasive thoracoscopic RRLC is combined with minimally invasive small lateral thoracotomy incision for CABG, RRLC combined with concurrent CABG surgery has entered the minimally invasive era [21]. The application of minimally invasive techniques reduces the risk of RRLC combined with concurrent CABG surgery, further improving the safety of the surgery. However, due to the lack of evidence for the long-term effects of minimally invasive CABG, this surgical procedure has certain limitations and requires more prospective cohorts for evidence. With the increasing maturity of da Vinci robotic surgery, how to apply da Vinci robots to RRLC combined with concurrent CABG surgery will be a future direction.

Perioperative management of RRLC combined with concurrent CABG surgery

We should pay attention to surgical indications before surgery and avoid adverse factors that affect the prognosis of concurrent surgery. A targeted intervention plan should be developed based on the specific situation of the patient before surgery. For patients with mid-term lung cancer combined with coronary heart disease, simultaneous surgery after preoperative neoadjuvant chemotherapy is safe and effective, which can reduce tumor marker levels and promote the patients' immune function and survival rate. During the operation, caution should be exercised, attention should be paid to protect the transplanted blood vessels, and sufficient hemostasis should be achieved before the end of the surgery. In addition, sufficient hemostasis before the end of surgery can avoid and reduce the risk of re-thoracotomy hemostasis, and early antiplatelet therapy will not increase the risk of re-thoracotomy hemostasis [22]. Some patients who underwent simultaneous surgery require adjuvant chemotherapy after surgery. There is currently a lack of systematic review on the use of targeted drug therapy and immunotherapy during the perioperative period of simultaneous surgery. Strict control of fluid intake and output is required during the perioperative period. If the infusion is excessive, it is likely to cause postoperative pulmonary edema and other lung injury problems. Therefore, the infusion rate should be controlled within 7-8 ml•h−1•kg−1 during the surgery, and it should be controlled within 1-2 ml•h−1•kg−1 after surgery. Meanwhile, maintaining a daily positive fluid balance of less than 1.5 L can effectively reduce the incidence

of postoperative complications [23].

The safety and long-term benefits of RRLC combined with concurrent CABG surgery

A meta-analysis study in 2014 showed that the mortality of RRLC combined with concurrent CABG surgery was 0–20.8%, and the mortality of staged surgery was 0–10.0%; the reoperation rate for bleeding in simultaneous surgery was 0–11.0%, while the reoperation rate for bleeding in staged surgery was 0%; the 1-year, 5-year, and 7-year survival rates of simultaneous surgery were 79.0–100%, 34.9–85.0%, and 61.0%, respectively; the 1-year and 5-year survival rates of staged surgery were 72.7% and 53.0%, respectively [24]. Since the included studies are all retrospective and dated, with a large time span and small sample size, there may be bias. Several recent cohort studies have shown no significant differences in the 5-year survival rate and 5-year tumor recurrence rate between staged surgery and simultaneous surgery [16,25]. The long-term survival rate of patients is mainly related to tumor recurrence and distant metastasis [26].

The comprehensive data analysis of a meta-analysis in 2021 showed that the mortality of combined heart surgery and lung tumor resection was low, and the incidence of complications was acceptable; subgroup analysis showed that OPCABG could reduce the incidence of complications [27]. At present, there are few prospective studies on lung cancer combined with coronary heart disease concurrent surgery, and more large-scale prospective studies may be needed to verify the long-term benefits of patients.

In conclusion, if we could strictly follow the indications for surgery, design a good surgical plan and strengthen perioperative management, RRLC combined with concurrent CABG surgery is safe, feasible, and effective, and could avoid many shortcomings of old-fashioned staged surgery (Figure 1).

Summary and prospects

With the aging of the population, the incidence of lung cancer combined with coronary heart disease shows an upward trend in recent years, and becomes an issue for oncology emergencies [28]. RRLC combined with concurrent CABG surgery is considered to be a safe and effective treatment method. The thoracoscopic RRLC combined with minimally invasive OPCABG through small lateral incision is currently the preferred surgical procedure, but due to the lack of evidence-based rationale for the long-term prognosis of minimally invasive CAGB, this procedure has limitations and requires more prospective cohorts for evidence.

The application of da Vinci robots in RRLC combined with concurrent CABG surgery will be a future direction. Current studies mainly consist of single-center retrospective analyses with small sample size and a very small number of single-center prospective cohort studies, lacking large-sample and multicenter prospective cohort studies. It is expected that more multicenter prospective cohort studies will be conducted in the future to validate the safety, feasibility, and long-term survival of RRLC combined with concurrent CABG surgery, and provide better evidence for clinical treatment.

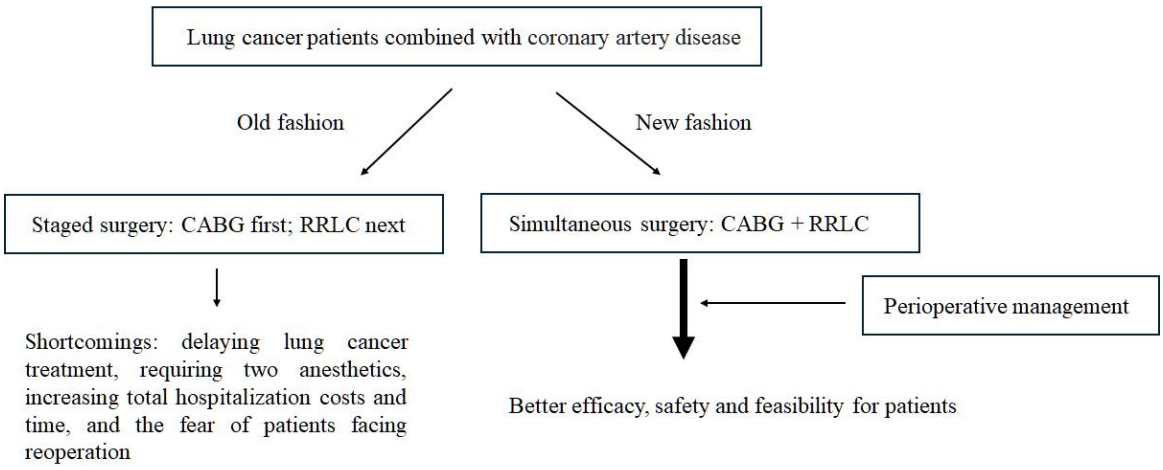

Figure 1. Comparison of old and new fashion for surgical treatment of lung cancer patients combined with coronary heart disease.

In old fashion, patients usually receive staged surgery with coronary artery bypass grafting (CABG) performed first and radical resection of lung cancer (RRLC) performed next. This procedure has many shortcomings such as delaying lung cancer treatment, requiring two anesthetics, increasing total hospitalization costs and time, and the fear of patients facing reoperation. In new fashion, patients receive simultaneous surgery with CABG and RRLC performed concurrently. With proper perioperative management such as sufficient hemostasis before the end of surgery, strict control of fluid intake and output, and appropriate infusion rate during the surgery, this procedure significantly improves the efficacy, safety and feasibility for surgical treatment of lung cancer patients combined with coronary heart disease

Conflicts of interest

All authors declare no conflicts of interest.

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