Role of surgery in NSCLC

When in doubt should we cut it out? The role of surgery in non-small cell lung cancer

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Will we ever really know whether surgery is effective in patients with resectable NSCLC?

Despite being a preventable disease, the public health impact of lung cancer is daunting. Lung cancer accounts for more than an estimated one million deaths each year. 1 Unfortunately, most persons with non-small-cell lung cancer (NSCLC) have unresectable disease at presentation with an overall 5 year survival rate of approximately 15%. 2,3 In contrast, 99% of patients with prostate cancer, 88% of those with breast cancer and 63% of patients with colon cancer are alive at 5 years. 4 For early stage NSCLC the preferred treatment is surgical resection, with an estimated 75 000 procedures performed in the US and 3000 in the UK each year. 5 This preference is supported by favourable 5 year survival rates for patients with potentially resectable tumours (stage IA 67%, stage IB, 57%, stage IIA 55%, stage IIB 39%). 6 However, up to 30% of patients with stage I and 65% of patients with stage II cancers will experience recurrence within 5 years of resection. 6 Furthermore, although recent survival rates for resected stage I and II disease have increased compared with historical controls, 7 this has been attributed in part to more careful surgical lymph node analysis (stage migration), 8,9 and the detection of earlier disease (lead time bias). 10

Surgical resection of lung cancer with intent to cure was introduced in the early 1930s by Graham and Singer. 11 Surgery was quickly accepted as the clinical standard of care for local stage disease, controversy still exists regarding the optimal surgical technique. In order to clarify this controversy, Wright and colleagues 12 identified studies that compared various surgical approaches. For example, the authors identified three randomised trials that assessed the survival benefit of radical lymphadenectomy compared with lymph node sampling at resection. 13-15 Individually, these three studies showed no statistically significant survival benefit for patients receiving complete mediastinal lymph node dissection. However, Wright and colleagues showed that the pooled hazard for overall mortality in patients receiving systematic nodal dissection was significantly reduced (0.78; p = 0.005).

Unfortunately, this conclusion is tempered by the considerable evidence of study design bias in these three studies. In two of the studies 13,15 an intention-to-treat analysis could not be performed due to post-randomisation exclusions, a bias that tends to favour the treatment arm especially in the setting of a meta-analysis. 16 Specifically, some of the patients were excluded due to upstaging following radical lymphadenectomy (stage migration). 17-19 Stage specific survival benefits due to stage migration during complete lymph node dissection have been observed in randomised trials of both gastric 20 and breast cancer 21 patients. Furthermore, two of the three studies 14,15 were unblinded during follow up assessment which may have resulted in a detection bias favouring the intervention. 15 Forthcoming results from a recently completed large randomised controlled trial conducted by the American College of Surgeons Oncology Group should provide more definitive evidence. 22

It is surprising that, despite the enormous public health impact of lung cancer, only 14 articles describing 11 randomised trials met the inclusion criteria following an extensive literature search. Some of the included studies did not report the mode of allocation concealment and none had a clear intention-to-treat analysis. These two study design biases are known to increase the magnitude of a treatment’s effectiveness. 23 None of the included studies
evaluated quality of life, performance status, or costs. The assessment of quality of life measures is now fundamental in the evaluation of lung cancer treatment outcomes.21 22 31

Given the dearth of patients studied and apparent study design weaknesses in most trials, is it possible to infer whether surgery is beneficial? For example, the only study that compared surgery alone with a non-surgical intervention (radiotherapy) had inconclusive results.33 In another study that enrolled patients initially assessed as inoperable but who were operable after radiotherapy, no significant difference in disease free or overall survival was found between the surgical and non-surgical control groups, although significant respiratory complications were noted with surgery.34 However, the lobectomy group also trended towards more surgical complications. Given the lack of indirect evidence of a surgical benefit, one might quibble with the assertion by Wright and colleagues that “by inference, some surgery might be better than no surgery”. Better designed and appropriately powered randomised trials are needed to establish definitively whether radical lymphadenectomy (versus lymph node sampling) or lobectomy (versus limited resection) are the preferred surgical techniques.

One must therefore ask whether we will ever really know whether surgery is effective in patients with resectable NSCLC. In the absence of well designed randomised trials, one might be tempted to rely on the results of observational studies to assess the efficacy of surgical resection for local stage disease. However, the key element that differentiates observational from randomised controlled trials is the potential for selection bias. Unfortunately, measures to control for selection biases in observational studies of surgery have not been sufficient. For example, a retrospective study in patients with stage I disease compared 291 surgically treated patients with 45 patients who did not undergo surgery and found substantially higher 5 year survival rates in the patients who underwent surgical resection (70% v 10%).35 However, the patients who underwent surgery were younger and had less medical co-morbidity, two confounding factors that were not specifically controlled for. Future observational trials should incorporate propensity scores or other sophisticated statistical methods to deal with overt bias and use appropriate sensitivity analysis to deal with potential hidden biases.

The preferred moral basis for performing a randomised controlled trial is clinical equipoise. Equipoise requires that genuine uncertainty exists throughout the medical profession with regard to the best treatment strategy.36 Because most clinicians believe that local stage disease is potentially curable with surgery, designing a randomised trial that includes an untreated control arm is highly problematic and probably unethical.37 However, equipoise for performing a trial of surgery versus no treatment might exist in certain limited circumstances—for example, in elderly lung cancer patients who present with relatively small ground glass opacities.38 39 Another way of achieving equipoise is a “preference trial” in which only those patients who are indifferent in their preference for treatments—that is, surgery v radiation, or surgery v best supportive care—are randomised.40 Currently, up to 30% of patients with early stage disease are either not offered or choose not to undergo surgery.41 In the future it should be a priority to perform studies (clinical equipoise exists) that compare traditional surgery with newer less invasive techniques such as stereotactic radiation and radiofrequency ablation. At the very least, we owe it to our patients to discover which surgical and minimally invasive techniques have risk to benefit ratios that are most favourable.


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Diagnosing CF: sweat, blood and years

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Use of algorithms for the diagnosis of CF

The diagnosis of cystic fibrosis (CF) is usually straightforward. The accepted criteria for the diagnosis of CF is one phenotypic characteristic of CF (such as lung disease or pancreatic malabsorption), or a positive neonatal screening result, or a positive history of CF in a sibling. For such children a sweat test is the most sensitive investigation to confirm the diagnosis of CF. The two algorithms provided in this issue of *Thorax* will also help in addressing the question: “Is this disease CF?” For example, in patients presenting with symptoms of bronchiectasis and recurrent respiratory tract infection, the diagnostic algorithms may be helpful in making the diagnosis of CF or excluding the diagnosis of CF. The algorithms provide a helpful approach to making the diagnosis of CF or neonatal screening for CF, most children present in the first year of life with failure to thrive, a number of the classic CF phenotype. Class 4 (e.g. RI117H) and class 5 (e.g. 3849+10kbC→T and IVS8-5T) are associated with altered chloride conductance of CFTR or reduced expression and with mild phenotypes. There are, in addition, a number of CFTR polymorphisms associated with mild phenotypes, particularly the number of TG repeats in IVS8.4

The most important investigation to confirm the diagnosis. Some patients also present with clinical disease later in childhood and into adult life and diagnosis can be more difficult for a number of reasons. In late diagnosed patients there is a wider range of presenting phenotypes in addition to the common presentations with respiratory infection and pancreatic malabsorption. Some present with single organ pulmonary disease (bronchiectasis), pancreatitis, severe sinuitis, or infertility. The explanation for this is that some mutations of the CFTR gene are associated with an atypical phenotype, usually with less severe lung disease. Over 1000 mutations of the CFTR gene have now been described, but only a proportion are associated with disease.4

Mutations of the CFTR gene which cause disease can be classified as follows: class 1, defective protein synthesis (e.g. G542X); class 2, defective protein processing (e.g. DF508); class 3, defective protein regulation (e.g. G551D). These three classes are considered to be severe mutations and are associated with the classic CF phenotype. Class 4 (e.g. RI117H) and class 5 (e.g. 3849+10kbC→T and IVS8-5T) are associated with altered chloride conductance of CFTR or reduced expression and with mild phenotypes. There are, in addition, a number of CFTR polymorphisms associated with mild phenotypes, particularly the number of TG repeats in IVS8.4

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At the most mild phenotypic extreme are people with congenital bilateral absence of the vas deferens (CBAVD) who have one or two mutations of the CFTR gene. The vas deferens is the most sensitive organ to CFTR dysfunction. About 50% of men who present with infertility and who have CBAVD have one or two mutations of the CFTR gene.4–7 They may have a sweat chloride level of 30–60 mmol/l and a slightly increased sweat chloride concentration. Single organ disease such as CBAVD, recurrent pancreatitis, or severe sinuitus. Such patients may have a single mutation of their CFTR gene and a normal or slightly increased sweat chloride concentration. Single organ disease such as this should not result in a diagnosis of CF, either classic or non-classic, and may be classified according to a WHO diagnostic list, though this is not an exhaustive list of diagnoses. The algorithms will also help in confirming the question: “Is this disease CF?” For example, in patients attending a general respiratory clinic (paediatric or adult) with symptoms of bronchiectasis and recurrent respiratory tract infection, the diagnostic algorithms may be helpful in making the diagnosis of CF or excluding the diagnosis of CF. The algorithms will also help in confirming the question: “Is this disease CF?” For example, in patients attending a general respiratory clinic (paediatric or adult) with symptoms of bronchiectasis and recurrent respiratory tract infection, the diagnostic algorithms may be helpful in making the diagnosis of CF or excluding the diagnosis of CF. The algorithms will also help in confirming the question: “Is this disease CF?” For example, in patients attending a general respiratory clinic (paediatric or adult) with symptoms of bronchiectasis and recurrent respiratory tract infection, the diagnostic algorithms may be helpful in making the diagnosis of CF or excluding the diagnosis of CF. The algorithms will also help in confirming the question: “Is this disease CF?” For example, in patients attending a general respiratory clinic (paediatric or adult) with symptoms of bronchiectasis and recurrent respiratory tract infection, the diagnostic algorithms may be helpful in making the diagnosis of CF or excluding the diagnosis of CF.