

Making a Difference in Surgery

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When asked what motivates them in their work, one commonly given answer by many doctors and surgeons is the feeling that they are “making a difference” for their patients.¹ Surgery uniquely rewards those who practice it diligently with the satisfaction that their efforts can directly determine the difference between life or death, wellness or suffering for those they care for.

It follows that conscientious surgeons strive to constantly improve their craft, so that they can make even greater differences in outcomes. For many surgeons around the world, inspiration for such improvements can usually be found in the pages of quality surgical journals – such as *Esculapio*. In such journals, reports of the latest clinical and academic research are mixed with descriptions of how interesting diseases and patients were managed. Presentations of major trial findings at international surgical meetings are another rich source of new knowledge. For those looking for clues to self-improvement, the most readily appreciated articles and presentations are often those that describe the latest surgical techniques and technology. These are cornerstones of modern surgical practice, and it makes sense that the modern surgeon is most easily attracted by the newest developments in these areas. However, it is perhaps time for surgeons to pause and recalibrate. Exciting as they may be, are advances in techniques and technology really the best way to make a difference in surgery today? Or are there other less glamorous – but perhaps more effective – ways in which surgeons can improve the lot of their patients?

In addressing this question, let us consider the author's specialty: Thoracic Surgery. Over the past year, what were the studies that really had the potential to allow thoracic surgeons to make a better difference?

In 2021, unarguably the most talked about study in Thoracic Surgery was the JCOG0802 trial from Japan, the results of which were first reported at the 2021 Annual Meeting of the American Association for Thoracic Surgery.² This was a high quality, nationwide trial in which 1108 patients with stage IA peripheral non-small cell lung cancer (NSCLC) with tumors no larger than 2cm were randomized to

receive either lobectomy (the current gold standard) or a segmentectomy (which preserves more lung for the patient). The surprising key finding was that segmentectomy gave not equal effectiveness as lobectomy – as many predicted – but a significantly *better* 5-year overall survival. The Japanese authors concluded that their results “indicate that segmentectomy should be the standard surgical procedure instead of lobectomy for patients with small-sized ... peripheral c-stage IA NSCLC”. This conclusion is in stark contradiction to current paradigms that dictate lobectomy is superior. This study quickly became the subject of fervent discussion in Thoracic Surgery communities around the world, and for the latter half of 2021, hardly any Thoracic Surgery conference was held without heated debate over what this trial meant for the future of lung cancer surgery.³ If it were true, then every lung cancer surgeon would be compelled from now on to completely change their practices when treating a large proportion of their lung cancer patients. The implications for surgeon re-training and re-tooling would be huge, and this led to near-anxiety amongst some surgeons.

This massive response by Thoracic Surgeons is actually not difficult to understand. Surgeons rely as said on technique and technology as the fundamental tools of their trade. A much-anticipated and rigorously conducted trial such as the JCOG0802 that informs surgeons that their current technique (lobectomy) is now obsolete is inevitably going to make huge waves. Because such a trial directly targets the center of surgical attention (technique), the immediate perception is that its findings are going to make a big difference for both surgeons and their patients.

As the results of the JCOG0802 trial gradually became digested, however, a calmer – but perhaps not clearer – picture emerged. Segmentectomy did produce better 5-year overall survival than lobectomy statistically, but the absolute difference in the study arms was only 3.2%.² This difference translates to 25 more deaths in the lobectomy arm. However, 19 of those 25 excess deaths were due to development of another cancer unrelated to the original NSCLC.² It is

perhaps bizarre to speculate that segmentectomy could somehow 'protect' patients against future cancer. On the other hand, despite the lower overall survival, segmentectomy in the JCOG0802 trial was shown to be significantly associated with a significantly higher rate of recurrence of the original lung cancer (12.1% versus 7.9%, $p=0.02$).² The presumed advantage of segmentectomy over lobectomy is in the preservation of lung function for the patient, but the JCOG0802 trial demonstrated that post-operative drop in lung function in the segmentectomy arm was only 3.5% less than in the lobectomy arm.² Though statistically significant again, in absolute terms the typical patient is highly unlikely to feel such a tiny difference in daily life. Therefore, when the data are analyzed, segmentectomy is actually not portrayed so overwhelmingly better by this trial, and the initial furor appears possibly overblown.

This is not to say that JCOG0802 is not a hugely important study. Even if the findings are taken to show segmentectomy as equivalent to lobectomy instead of superior, it would be a massively significant study in Thoracic Surgery. Instead, the purpose of highlighting the controversy over this trial is to show how surgeons are so readily drawn into hyperbolic reactions over reports pertaining to technique and technology because there is a perception that these are the areas where a difference is most likely to be made. In reality, this is nowadays rarely the case.

In the 1990s, the advent of Video-Assisted Thoracic Surgery (VATS) as the minimally invasive approach for chest surgery represented a quantum leap forward and revolutionized the specialty.^{4,5} This was because the previous gold standard – open thoracotomy – was such a traumatic and debilitating approach that any move towards 'keyhole' surgery could easily be shown to reap benefits in comparison. This led to the belief that progress in techniques and technology could make the difference sought after. However, modern VATS is now so well-developed and efficacious in minimizing post-operative morbidity that showing a difference when using any 'newer' approach is dauntingly difficult.⁵ Over the past 10 years, many surgeons – including this author – have tried to improve upon conventional VATS using multiple ports by evolving to 'single port' or Uniportal VATS.⁶ However, even today it has been frustratingly difficult to definitively prove that Uniportal VATS is comprehensively better than the older techniques.⁷ This is simple because the limiting factor in patient outcomes is no longer the surgical technique per se. Instead, other areas of the surgical experience hold

much better promise for surgeons wishing to make a better difference for patients. For example, implementing a good Enhanced Recovery After Surgery (ERAS) clinical pathway has been shown to yield much greater improvements in patient recovery than Uniportal VATS.⁸ Sadly, advances in non-technical areas (ERAS) are never as 'sexy' or appealing as technical advances (Uniportal VATS or robotic surgery) for most surgeons – and hence the former tends to get neglected.

Coming back to 2021, one could ask: if technical advances such as segmentectomy weren't the real area to look in for making a better difference in Thoracic Surgery, then what were? For that, this author would draw attention to another class study: multi-modality lung cancer therapy. The key representative of this field in 2021 is perhaps the IMpower010 trial.⁹ This was a phase 3 international study of atezolizumab vs best supportive care after adjuvant chemotherapy in resected Stage IB-IIIa NSCLC, the results of which were reported at the 2021 Annual Meeting of the American Society of Clinical Oncology. While some academic Thoracic Surgeons will be very familiar with this study by now, the majority who know about JCOG0802 will likely be completely unaware of the implications of IMpower010, or may have not even heard of it entirely. The reason for this may well be that IMpower 010 was announced at an oncology – not surgical – meeting. However, it is possibly more likely that IMpower010 simply dealt with a topic (immunotherapy) that had nothing to do with surgical technique or technology. This would automatically put in under the radar for most surgeons. In the world of Oncology, IMpower010 was instantly recognized as a landmark trial, but most Thoracic Surgeons probably missed that this study had greater potential to make a difference for their patients than any advance in operative technique or technology.

The IMpower 010 trial randomized over 1000 patients Stage IB-IIIa NSCLC who had received both complete surgical resection and 1-4 cycles of adjuvant chemotherapy to receive either atezolizumab or best supportive care.⁹ The results indicated a 34% reduction in risk of disease recurrence or death with adjuvant atezolizumab in the PD-L1 TC $\geq 1\%$ stage II-IIIa population (HR, 0.66; 95% CI: 0.50, 0.88). On this basis of this finding, on October 15, 2021, the American Food and Drug Administration (FDA) approved atezolizumab for adjuvant treatment following resection and platinum-based chemotherapy in patients with stage II to IIIa NSCLC whose tumors have PD-L1 expression on $\geq 1\%$ of

tumor cells.¹⁰

In itself, this represented a new and important addition of immunotherapy for the management of NSCLC. However, in a broader perspective, IMpower010 was the latest in a number of groundbreaking studies ushering in the era of multi-modality lung cancer therapy. In 2020, the ADAURA study already breath-takingly demonstrated that the addition of osimertinib as adjuvant therapy vastly improved disease-free survival after surgery in patients with Stage IB-III A NSCLC compared to standard chemotherapy alone.¹¹ Strikingly, even patients with stage IB disease could potentially now benefit from adjuvant target therapy, and this had great implications for surgeons. In 2021, studies such as CheckMate-816 also suggested that immunotherapy could be potentially effective as neoadjuvant therapy.¹² In this randomized phase 3 trial, 358 patients with resectable stage IB-III A NSCLC received either neoadjuvant chemotherapy or neoadjuvant nivolumab plus chemotherapy, and then proceeded to have surgical resection. The trial found that adding the nivolumab significantly increased the depth of the pathological response by the time of surgery. Subsequently announced interim analysis further suggested that nivolumab plus chemotherapy showed a statistically significant and clinically meaningful improvement in event-free survival compared to chemotherapy alone when given before surgery.¹³

When put together, these studies all point to the same new reality: that we are now truly in the era of multi-modality therapy for NSCLC. No longer can surgeons and oncologists expect to treat patients separately [14]. Before the advent of modern target therapy and immunotherapy, adjuvant and neoadjuvant therapy for lung cancer provided survival benefits that were statistically significant, but only marginally better in absolute terms.^{15,16} However, these new trials show that using target therapy and immunotherapy in the adjuvant and neoadjuvant settings afford very real advantages in survival.^{9,11,12} This is truly making a difference for patients. This difference is made not through injecting technique or technology per se into surgery, but by adapting to working ever more closely with oncologists in an MDT environment. The surgeon who may have previously pictured him- or her-self and as a lone superhero will now have to get used to being in a team of different heroes like the *Avengers*.

These recent target therapy and immunotherapy may also lead to other less obvious implications. Given the benefits of these new adjuvant and neoadjuvant therapies, there is added impetus for offering genetic mutation and biomarker testing in even earlier stages of disease. There is a compelling argument that most – if not all – lung cancer patients now should now be routinely discussed at multi-disciplinary team (MDT) meetings, including those with stage I disease.¹⁴ At the other end, the debate over the role of surgery in stage III A disease should perhaps now shift firmly in favor of more surgery. If these new adjuvant and neoadjuvant therapies can so effectively improve oncological outcomes after surgery, thresholds for operating in selected patients should perhaps come down.

Furthermore, for patients with stage III A disease but a favorable genetic mutation and biomarker profiles, surgeons at an MDT discussion could assert with a louder voice for upfront surgery followed by adjuvant therapy. Traditionally, guidelines tend to favor neoadjuvant therapy before surgery for resectable stage III A disease.¹⁷ However, with neoadjuvant chemotherapy, there is a substantial pre-operative attrition rate, whereby a proportion of patients referred for neoadjuvant therapy never ultimately receive surgery for various reasons (such as adverse events and complications, or disease progression).¹⁸ It has previously been estimated that up to around 70% of such patients do not receive surgery.¹⁸ The recent studies above suggest that if post-operative adjuvant target therapy and immunotherapy can be very effective,^{9,11,12} then maybe it makes sense for select patients to promptly receive surgery first instead of induction or neoadjuvant therapy first.

The significance of the era of multimodality therapy is that this strategy benefits a huge range of patients with stage I to stage III A disease. The latest target therapies and immunotherapy potentially allow surgeons to reach even patients with later stages of lung cancer, broadening the scope of who may receive curative resection. The benefits gained by each patient is potentially a marked step up in terms of survival – the most pertinent metric of all for lung cancer patients. However, the studies that show the way towards this may not appear as exciting or attractive to surgeons. Instead, the studies that focus on techniques and technology continue to grab the attention of most surgeons. Which surgeon would not be captivated by flashy surgical videos or hi-tech new gadgetry? But on closer scrutiny, these advances tend

to only apply to patients with early-stage disease within significantly reaching a broader range of patients. They also tend to give minor benefits in terms of lowering surgical morbidity, without actually giving gains in terms of survival.

For surgeons of any specialty – not only Thoracic Surgery – it behooves us all to remember this simple message. If the goal is to make a difference for our patients, then we should look beyond the glitz of fancy techniques and mesmeric technology. Surgeons should pay more attention to the less glamorous but more profound clinical research that can help more patients and in more meaningful ways.

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