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Citation: EMJ. 2025;10[4]:57-59. https://doi.org/10.33590/emj/KXXU9885

Q1 With the widespread adoption of lung cancer screening, we are diagnosing more cancers at sub-centimetre, preclinical stages. How has this shift from late to early detection changed the surgical philosophy from radical resection toward minimal, biologically informed intervention?

One thing that we're seeing is lung cancers being diagnosed earlier and earlier, whereas, historically, 75% of lung cancers were diagnosed at Stage IV, which is when they've already spread. Now, we're seeing the stages shifting. Historically, lobectomy, which is the removal of about 20–25% of someone's lung volume, has been the standard of care, but now if we catch a tumour that is under a centimetre in size, one of the questions is, is that too much to take? There is a risk of those patients developing lung cancer in the remaining lung, so part of the strategy now is lung preservation and how we maintain that for these patients.

Separate from that are also the biologically aggressive cancers. We know that some of these small tumours can be aggressive, while some are not. How can we differentiate between these? Some patients with 3 cm tumours may just need surgery, while some patients may need chemotherapy, immunotherapy, or targeted therapy more than surgery. But that's what the future is about, understanding some of that nuance.

Q2 Tumour size and stage have long guided early lung cancer management. What emerging molecular or genomic markers, such as specific driver mutations or tumour mutational burden, do you think will be key to defining a true precision classification for Stage I non-small cell lung cancer?

I think we'll see a difference in practice patterns in the future, where all patients, even those with very small tumours, will have biopsies before surgery, even if we think they're amenable to surgery, that will be genetically tested. I think that will change as we go forward. Right now, we don't have molecular targets for every cancer, but if you look back 10–15 years ago, I think less than 50% of lung cancers had a driver mutation that we could identify. That has now changed more and more. If we get to the point where most lung cancers have an identifiable target, I think that personalised therapy will become a much more realistic option.

Q3 Circulating tumour DNA (ctDNA) and other liquid biopsy technologies promise to assess tumour biology non-invasively. How close are we to using ctDNA or similar assays to distinguish aggressive from indolent early lesions, and to guide whether a patient should undergo surveillance, ablation, or surgery?

There are a lot of different ways that we're going about that. One is through biopsy, but when diagnosing someone with lung nodules in advance, there are a lot of different options out there. I

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think there's still a lot of validation work being done in those spaces.

The other option is after surgery, but can we identify patients who, after surgery, still have residual ctDNA, and do those patients benefit from adjuvant chemotherapy or targeted therapy? There are a couple of companies in that space right now. We're currently evaluating the use of one of these tests routinely after surgery, though we have not started to test this routinely.

Q4 You have been directly involved in the development of lung ablation techniques. Where do you see ablation fitting into the treatment algorithm for early-stage tumours, particularly as we refine patient selection based on biology rather than just tumour location or operability?

I think that ablation therapy is a great option. Going back to that idea of minimally invasive treatment and how we can treat tumours that are under 1 cm in size, one of the challenges is if we can treat those tumours and ablate them with a single stage option. We've always had radiation therapy as an option for these, but now we have the ability to do a biopsy and ablate in the same setting and then track these patients, even if they have a very small lesion. Most likely they don't need a lobectomy, and even a segmentectomy or a wedge may not be necessary if we catch these early enough. The combination of ablation plus these circulating liquid biopsies is really going to change how we approach things.

Q5 Your prior work with David G. Beer, University of Michigan Medical School, Michigan, USA, explores novel molecular pathways such as checkpoint kinase 1 (Chk1) in lung cancer. How might pathway-specific targeting, whether Chk1 or others, translate into actionable therapies for early-stage disease, perhaps in the neoadjuvant or adjuvant setting?

Chk1 is a precursor for PDL1. It was interesting as, when we did that, there were no Chk1 inhibitors on the market, and they were not being supported for research, so we stopped doing that research. But then a lot of work shifted to PDL1, which is on the same pathway.

That's where a lot of the investments have gone. It's all related in terms of the immune-stimulation aspects. If we talk about driver mutations, either a liquid biopsy or doing a percutaneous/needle biopsy of the tumour can help us understand what the driver mutations are. Then we can treat them, and we know that some patients are going to be at high risk for recurrence or spread, while some are going to be low risk. So, maybe we treat those high-risk patients with 1 cm tumours with a high-risk driver mutation and a high level of aggressiveness.

Right now, we would just treat those patients with surgery and surveillance. So, I think there will be game changers in terms of how we approach that. But it depends on the market, and there are different levels of regulatory clearance in the USA, Europe, and Asia. Those will be some differences in terms of challenges. There is also the associated cost. There are different investments in

different countries and regions for prevention or surveillance.

Where I live in Michigan, USA, which is a state of about 10 million people, I think we estimate that less than 10% of people who should be getting lung cancer screening are getting screened. So, that's where I think we need to go first. And I think that, if we can make inroads there, we'll see growth in terms of all these other needs. I think it's going to be a stepwise approach.

I wish I could say that in 2 years we'll be there, but I think it may be a little closer to 10 or 20 years.

Q6 As imaging and AI evolve, do you see a role for computational models in predicting tumour behaviour or treatment response, essentially creating a 'digital biopsy' that could complement or even replace tissue-based diagnostics?

I do. The challenge there is how you frame AI versus machine learning. I think we do a lot of those things already, and I believe it'll have a role. In terms of how that will be defined, I've been a part of some grant proposals looking at AI interpretation of radiology film and CT scans of the chest to try to do that. Those have not been funded, but I know other people are working in that space.

Q7 You have highlighted the importance of quality of life and long-term functional outcomes. How can we better standardise quality of life assessment across trials comparing minimally invasive surgery, stereotactic radiotherapy, and ablation for early-stage disease?

So, there are studies and parameters in terms of how to do that. We measure breathing function and similar things. I think patient reported outcomes and quality of life will be critical in terms of assessing all of these future treatment plans. But we know that patients will prefer minimally invasive surgery. I think the proof is there on patient preference, but now we have to prove similar long-term efficacy and then balance that against the quality-of-life benefits.

Q8 If you could drive one major change in the global management of early-stage lung cancer, whether in clinical practice, research direction, or policy, what would it be and why?

I think it's really about encouraging lung cancer screening. I think that's the lowest hanging fruit. Lung cancer screening rates are still abysmal for patients who really need it. I think there is a potential role for expanding the criteria as well, but we first have to get to the people who are in the current criteria guidelines. If we can do that, I think we would see a huge shift towards earlier and earlier stage lung cancers, which can be treated with surgery. If we also bring in these personalised therapies, it will make a real impact in terms of making lung cancer more of a chronic disease rather than a death sentence, which it historically has been for most patients.