INTERVIEW

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Lung cancer: a very challenging disease

Philippe Lambin* speaks to Alisa Crisp, Commissioning Editor:

Philippe Lambin is a clinician, a radiation oncologist, and a pioneer in translational research with a focus on hypoxia and Decision Support Systems. He has a PhD in radiation biology and is professor at the University of Maastricht (radiation oncology) and at the University of Eindhoven (functional imaging). He is co-author of more than 282 peer-reviewed scientific papers (Hirsch Index: 42), co-inventor of more than 13 patents (filed or submitted) and (co)promotor of more than 27 completed PhDs. Moreover, Professor Lambin has

extensive experience with clinical trials. He is one of the international experts in the Flims workshop 'Methods in Clinical Cancer Research' organized jointly by the Federation of European Cancer Societies, American Association for Cancer Research and American Society of Clinical Oncology and he is leading several clinical trials. He is also a member of the scientific committee of Koningin Wilhelmina Fonds (the main Dutch funding body in cancer research) and the advice committee on proton therapy of College Voor Zorgverzekeringen (Dutch medical insurance). He is currently involved in several successful European grants (e.g., Centre for Disruptive Photonic Technologies, Biocare, Euroxy, Metoxia, euroCAT and Eureka) and one NIH grant (in radiomics). His main areas of interest are directed towards translational research in radiation biology with a specific focus on tumor hypoxia, functional imaging (computed tomography-PET) and lung and head and neck cancer.

Q What led you to a career in radiation oncology & lung cancer?

When I was young, my ambition was to work in developing countries and in fact, over the past few years, I have been working in the Ivory Coast and Bolivia. On returning from these countries, I decided to choose a specialty that would be cutting edge and pose a real challenge. I first chose to specialize in oncology and then specifically in radiation therapy because there are three components: a clinical component based on patient care, which works across different diseases; a technological component, which is quite challenging (and in this sense, we have seen enormous changes in technology in the last 20 years); and

the third was a biological component that I found very attractive having completed my PhD in Biology at the Institut Gustave Roussy in Paris (France).

Lung cancer is a really challenging disease. Cancer is the leading cause of death in western countries and lung cancer is the leading cause of cancer-related death among those. It is also a rather complicated disease, at least for radiation oncologists, because there are very sensitive organs around the tumor and frequently the tumor moves with the breathing cycle. Therefore, I was attracted by the challenge and the fact that there was still a lot of room for improvement. When I started my training, the radiation of lung cancer

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News

Journal Watch

Interview

*Maastricht Radiation Oncology (Maastricht), GROW Research Institute, Maastricht University, Maastricht, The Netherlands; philippe.lambin@maastro.nl

was used especially for palliative treatment using rather simple irradiation techniques, whereas with modern equipment, it has now become more and more of a curative treatment: for stage 1–2 (non-)small-cell lung cancer, and even for stage 3 inoperable cancer, stereotactic radiotherapy is frequently replacing surgery.

Q Which clinical trials have been the most important among those that you have been involved with?

I believe in two types of clinical research: first, the conventional clinical trials; and second, the new trend that is called ‘rapid learning healthcare’, which is where medics try to gain knowledge from all the routinely treated patients. This makes it possible to gather information from more individuals: usually only up to a third of patients are included in medical trials and they are often not representative of the real population. Therefore, it is also important to gather knowledge of the whole population, for example, how to treat elderly patients. At the moment, I am involved in conventional clinical trials, such as dose-painting trials, which are rather important, imaging trials, which focus on imaging biomarkers, and some trials that are targeting tumor hypoxia. For example, there are trials evaluating the effect of chloroquine, the antimalaria medication that inhibits autophagy, and the use of the nitroglycerin patch, which hypothetically improves diffusion and reduces hypoxia in lung cancer. The chloroquine and the nitroglycerin trials are interesting because they are based on drugs that are not covered by a patent; one could think that they are easy trials to carry out because these drugs are very cheap, but in practice it is exactly the opposite. It is very hard to get funding for these trials because pharmaceutical companies are not interested in funding them. The European community should consider funding these trials, which could be very important for society because the drugs they use are very cheap and the toxicity is well known.

Q Could you describe what you are looking for in dose-painting trials?

Initially, we irradiated lung tumors in a homogeneous way, which is the standard

of care. By systematically doing PET scans 3 months after treatment to evaluate metabolic response, we identified some areas within the tumors that have a high affinity for fluorodeoxyglucose. These areas are more therapy resistant, so what we try to do is see whether we can improve the outcome by increasing the dose on the high fluorodeoxyglucose, so the more therapy resistant areas of the tumor can be targeted. We really need to move away from the simple approach of ‘gross tumor volume plus biological tumor volume to be irradiated with margins’. We need to do more research in dose painting of normal tissues, use uncertainty-based planning (see the work of Fontanarosa *et al.* [1]) and consider other target volumes such as ‘normal tissue avoidance volume’ and ‘GTV low drug uptake’.

Q Talking about your current research, what other projects are you currently involved in?

I am involved in a so-called ‘rapid learning healthcare project’, through which we are trying to build decision support systems to improve them by adding a molecular marker to the existing clinical-based decision. This will happen by adding blood or imaging biomarkers to predict survival. We are also carrying out trials where we are trying to kill specifically hypoxic cells in the tumor because we know that hypoxic cells are the cause of therapy resistance in chemoradiotherapy-based treatments. Recently we have introduced the concept of ‘radiomics’, the high-throughput extraction of large amounts of image features mostly from standard radiographic images that holds great promise, but needs further validation in multicentric settings and in the laboratory [2]. Furthermore, we are involved in trials of radiation combined with targeted drugs such as CAIX inhibitors, a fascinating quite new therapeutic target, bioreductive drugs (e.g., TH302) and immunomodulators. The last one is of particular interest because there is evidence that radiation induces ‘immunogenic death’, synergizing with immunomodulators such as L19-IL2 and/or inhibitors of immunologic checkpoints.

Q What kind of question is it important to answer in the rapid learning healthcare project?

The project is focused on building predictors of outcome and toxicity, and to validate these predictors so that when a new patient arrives, we can apply them and try to choose the best option. In other words, we are trying to build a decision-support system, created from different predictive algorithms for survival, regional control and lung and esophageal toxicity.

Q Could you tell us more about these decision support systems & how they work?

I believe that in the future it will be compulsory to use these systems to make the final decision about treatments because the treatments are becoming more individualized and there are more options. Moreover, considering what the patients really want is recognized as an important factor. We know that doctors have difficulties when they have to make decisions where there are more than five variables involved. Thus, what we are trying to do is to build multifactorial decision support systems including clinical imaging, treatment and psychological variables [3].

A good example is the inoperable non-small-cell lung cancer for which the TNM classification is not prognostic. If you make the decision for either a curative or palliative approach based on the TNM classification, which is often described as the correct way to proceed in the guidelines, it actually becomes a random process, and therefore unethical. We believe that simple decision support systems, such as the ones described, can really help to make progress in daily care [10].

Q Has there been any evidence for the use of these systems so far?

We have validated these decision support systems in different settings. Recently, we have completed prospective validations where we compared the prediction of the doctors and the prediction of the model and we found that the model was superior to the doctors' prediction systematically. Therefore, that was very important proof that these models, which are quite cheap

to use, have good value and we hope that we will now get funding for randomized controlled trials comparing patients treated based on guidelines versus patients treated according to model-based systems.

Some doctors are already using these systems in their hospitals: we have received messages from treated patients who said that originally they would have been considered for palliative treatment, but instead, thanks to our model, they have received curative treatment and they are still alive; so these decision systems are already used in the clinic. Models will be used mainly when it will be legally compulsory or when the specific type of therapy will be linked to the use of these models, which will be the case for proton therapy in The Netherlands. Thus, in 4 years you will only be able to get reimbursement for proton therapy in place of conventional radiotherapy, if you can prove with these models that the patient is likely to benefit from this more expensive treatment option.

Q How do you see this impacting the role of the clinician in managing lung cancer patients in the future?

Clinicians will have more time to spend planning and remodeling the management of patients; moreover, the models are designed to better involve the patient in the decision. It is a big problem if you want to base your treatment plan on what the patient wants, but you are not able to predict the outcome of the different possible treatments. Instead, if you can say with relative certainty what will be the outcome of the different treatments – survival, local control, dose or complications – then it will be easier to involve the patients in shared decision-making; in a way, models will facilitate shared decision-making, involvement of the patient in the decision and hopefully also good relationships between patients and doctors.

Q You have created other computer systems for delineating tumors in CT scans: could you tell us more about these systems?

One of the weak points in the radiotherapy workflow is the delineation of the tumor. This aspect is crucial because if you miss

part of the tumor and you do not irradiate it, then the patient will surely relapse. On the other hand, if you are not precise enough with your delineation you will irradiate a significant volume of normal tissue with a high dose, so it is important to have automated systems validated by pathology that can improve the workflow and hopefully decrease the volume of normal tissue that is unnecessarily irradiated.

There are now some computer models that extract imaging features from abnormal lesions and can say how likely it is to be cancer. In terms of using these systems for radiation planning, automatic delineation systems will be an easy way to increase inter-doctor reproducibility and to speed up the workflow.

Q How important is stereotactic body radiation therapy for lung cancer treatment?

It is a very important treatment because it gives similar results to surgery, but at lower morbidity and cost; in particular, it allows us to treat elderly patients, sometimes up to 85 years of age. There is some evidence from a group in Amsterdam (The Netherlands) that when they used stereotactic body radiation in elderly patients, they were more often treated with curative intent and the prognosis was improved [4]. Stereotactic body radiation is a very important development for small tumors that are technically operable but for which we cannot choose surgery because there are other concurrent diseases. Looking toward the future, I do not think that stereotactic body radiation will replace surgery, but it will be complementary to surgery for difficult cases, such as patients who are medically inoperable. Surgery will always have a place.

We are going to see an increase in people using stereotactic body radiation because it is cost effective and in the future, we will have more elderly patients. The technology will progress itself, although we must be aware that not everybody will have this type of treatment.

Q Can you tell us more about the state of proton therapy at the moment?

Worldwide we have some indication because we were using scattering proton

therapy. We are starting to use pencil beam scanning proton therapy, which allows motion management, which is very important for lung cancer. The motion management part is relevant because the lung moves with breathing and if that is not taken into account, then it is possible to do more damage than with conventional radiotherapy. In this area, we have made significant technological progress and at the moment there are randomized trials in the USA comparing proton therapy to photon therapy [102]. It is a very important trial even though it is not based on the most advanced motion management technology. My guess is that proton therapy is only suitable for approximately a third of patients. It is in cases like this in which the decision-support system is important to try to predict which patients will benefit more from proton therapy.

Q How do you see radiation therapy for lung cancer changing in the coming years?

In the coming years, radiation therapy will be based on multifactorial decision-support systems [3] in order to individualize treatment and include molecular and imaging biomarkers, particularly based on DNA sequencing. In the context of individualized medicine, I believe in the combination of radiation with targeted drugs (kinase, CAIX and Notch inhibitors), immunomodulators (e.g., inhibitors of immunological checkpoints) and, of course, hypoxic modifiers (bioreductive drugs and inhibitors of autophagy) after proper selection. I see a growing role for proton therapy for certain patients where it could be beneficial namely after selection with decision support systems. There will also be a more important role for precision radiotherapy, by measuring the dose *in vivo* in 3D, the so-called 'dose-guided radiotherapy' so that we will know exactly what we are doing to further improve the precision. As for technological advances, in the field of conventional photon therapy we are reaching a plateau. Perhaps there is still room for progression in dose-guided radiotherapy – that is, measuring the dose in 3D. Otherwise, there is still a lot to do in the field of proton therapy, dose painting

and its combination with targeted drugs. Furthermore, we will have to move towards shared decision-making because we already have level 1 evidence in favor of it [5]. We will have to rethink our methods to carry out clinical research, one way being rapid learning healthcare [6].

In short, I think that the future of radiation oncology in the western countries is bright, especially with the growing elderly population and the need to have cost-efficient treatment. The challenge will be to disseminate modern radiation oncology in the developing countries and to do this we will need to revolutionize our training approaches, for example with e-learning.

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