WHERE DO WE GO FROM HERE? FUTURE DIRECTIONS IN STAGE III PATIENT TREATMENT

Interview with David S. Ettinger, MD, Julie R. Brahmer, MD, and Edward S. Kim, MD

Dr Ettinger is The Alex Grass Professor of Oncology at the Johns Hopkins University School of Medicine. He is also Professor of Medicine, Otolaryngology, Head and Neck Surgery, Gynecology and Obstetrics, Radiation Oncology and Molecular Radiation Sciences. He is Associate Director for Clinical Research at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins. He has been a chairman of the Thoracic Committee of the Eastern Cooperative Oncology Group (1980–1982) and, since 1990, he has been chairman of the Medical Oncology Lung Subcommittee of the Radiation Therapy Oncology Group (RTOG). Dr Ettinger is an investigator on the Hopkins SPORE grant for lung cancer. He is a member of the National Comprehensive Cancer Network (NCCN) Board of Directors and a member of the NCCN Guidelines Steering Committee. A graduate of the University of Louisville School of Medicine, he completed his medical internship and residency at the Albany Medical Center and Mayo Clinic, respectively. Dr Ettinger completed his training in medical oncology at Johns Hopkins. He has been on the faculty of the School of Medicine since 1975. He received the American Cancer Society’s highest national divisional award, the St George Medal, in 1997. A primary investigator in many clinical trials addressing treatment strategies and anti-cancer agents, his interest is in new drug development and innovative multidisciplinary treatment strategies in lung cancer and sarcomas.

Dr Brahmer is a medical oncologist at Sidney Kimmel Comprehensive Cancer Center (SKCCC) at Johns Hopkins. She is Assistant Professor of Medical Oncology. She received her medical degree from the University of Nebraska Medical Center and completed her medical internship and residency at The University of Utah, where she was chief resident. She completed her fellowship training in medical oncology at SKCCC and then joined its faculty. Dr Brahmer’s research focuses on the development of new treatment strategies for lung cancer and mesothelioma, in addition to lung cancer prevention. Dr Brahmer is a principal investigator for several early stage clinical trials developing drugs for the future treatment of lung cancer. She is also the co-leader of 2 large national cooperative group trials using new targeted therapy with conventional chemotherapy for the treatment of non-small cell lung cancer (NSCLC) and using maintenance targeted therapy with conventional chemotherapy for the treatment of small cell lung cancer.

Dr Kim is a thoracic medical oncologist at the University of Texas MD Anderson Cancer Center in Houston. He is Assistant Professor of Medicine, Director of Educational Programs in the Department of Thoracic/Head and Neck Medical Oncology, and Director, Residency Training in Oncology at the University of Texas MD Anderson Cancer Center. He received his medical degree from the Honors Program in Medical Education at Northwestern University and completed his medical internship and residency in internal medicine at Baylor College of Medicine. He completed his fellowship training in medical oncology at MD Anderson Cancer Center and then joined the faculty. Dr Kim has received an American Society of Clinical Oncology Young Investigator Award and Merit Award, a career development award through the head and neck SPORE mechanism, and Scholar-in-Training Award from the American Association for Cancer Research. Dr Kim has led clinical trials studying novel biologic approaches in lung cancer and head and neck cancer, including treatment and prevention.
A senior clinical editor for Johns Hopkins Advanced Studies in Medicine (ASiM) interviewed Drs Ettinger, Brahmer, and Kim to get their reactions to specific ongoing controversies and to discuss more general concepts of the role of multimodality therapies and treatment options for patients with stage III NSCLC.

JHASiM: Please comment on the goal of the IASLC (International Association for the Study of Cancer) staging project.

Dr Ettinger: The IASLC agreed to establish an international staging committee in December 1998, they had their first meeting in June of 1999, and the UICC (International Union Against Cancer) accepted that the committee will be the primary source for recommendation for the seventh revision of the TNM classification to be enacted in January 2009. The recommendation must be presented to the IASLC board in late 2006. It will be passed on to the UICC in January 2007, and it’s based on a clinical TNM database (>40,000 cases) and a pathologic TNM database (>23,600 cases). The goals of the new staging are to make it global without bias by any one area of the world and to have it make sense in how we practice medicine, whether it be as a medical oncologist, radiation oncologist, or thoracic surgeon. I think a good example would be the satellite lesions in one lobe—that is, multiple lesions in one lobe—it would be classified as T4 stage IIIB. If there are no nodes, the surgeons will take out that lobe. That patient may do very well, yet that’s considered stage IIIB disease, which statistically has a poor 5-year survival rate. Most of us think that particular situation will change into a more appropriate stage. Thus, I think it is both what the treatment may be for a particular patient and what the prognosis would be based on the stage.

Dr Kim: The last restaging modification was in 1997. There were some very minor changes, but it still made an impact. The T3N0s migrated down to stage II, when previously they were stage III, plus you had to interpret older data differently, especially some of the adjuvant chemotherapy trials because the T3N0s were technically stage III at that time, but we all know they behave better as stage II. Therefore, sometimes the stage III numbers look a little better and the stage II numbers do not look as good.

JHASiM: What effect will changes in staging have on approaches to single or combined-multimodality therapy?

Dr Ettinger: If you can stage the patient accurately, then you can predict what the survival would be for that patient, and then the treatment will be planned accordingly. For example, for stage IA T1N0M0 we just do surgery. However, is there a group of patients that would do poorly? Also, a T1 lesion that’s 2.8 cm with a poorly differentiated tumor with vascular lesion is not going to do the same as a 0.5-cm lesion that’s well differentiated and no vascular lesion. Should patients with this T1 lesion and with these poor risk factors receive adjuvant chemotherapy?

I think those are the nuances that may or may not be addressed. We’re going to have a better understanding, based on the TNM staging, of where the patient’s stage of disease fits from the standpoint of prognosis, and then there is the treatment for a particular stage. Remember, the staging group does not tell you how to treat the patient.

Dr Brahmer: Hopefully, now the staging will actually reflect what we do. It will be more congruent with what we do and make more sense for the treating physicians and the patients.

Dr Kim: I don’t feel that the new staging project will change the effects on our modalities of therapy at this time. The ones that I can see moving are the T4, N0, or N1 patients. Those patients are considered stage IIIB, but many of those tumors are resectable. That’s the only staging I can see in the stage III that may move down, and thus we wouldn’t be resecting stage IIIBs anymore, which is more of an accurate classification and thus prognosis.

JHASiM: Is there a role for surgery in stage IIIA (N2) or stage IIIB NSCLC?

Dr Brahmer: I think for the stage IIIA (N2) disease there can be a role for surgery, but definitely with neoadjuvant therapy. It depends on whether the patient needs a pneumonectomy. For stage IIIB patients, it depends on why they’re IIIB. I think if they’re T4 then it totally depends on the patient. If you’re able to remove the vertebral body, or if you just have multiple small nodules within one lung or lobe, then you can consider surgery. However, if you’re IIIB because of nodal disease (N3), then I don’t think the patient is amenable to surgery.

Dr Ettinger: I would say yes, but there are many
factors involved. Remember, stage IIIB can be T4N0-3M0 or T1-3N3M0 (ie, N3 being supraclavicular nodes or contralateral nodes). You wouldn't do surgery there, but a T4 superior sulcus tumor can be a IIIB, and surgery may be of a multimodality approach with chemotherapy, radiation therapy administered first, possibly followed by surgery. Also, stage IIA is T3N1M0 and T1-3N2M0. Therefore, if you have big bulky disease and you could shrink down the nodes with chemotherapy or chemotherapy plus radiation therapy to essentially a normal computed tomography (CT) scan and a negative positron emission tomography (PET) scan, you've downstaged them and surgery may be part of the treatment. You then factor in age, the pulmonary function studies, and if the patient can tolerate a surgical procedure.

The RTOG 9309 Intergroup study looked at a multimodality approach to treating stage IIIA disease. This study looked at radiation (4500 cGy) plus etoposide platinum and randomized between surgery and additional radiation followed by additional chemotherapy. In patients who had pneumonectomy, 26% of them died. Yet, patients that had lobectomy did better plus survived longer free of disease. Therefore, it depends on the patient population, the amount of disease, and a host of other factors.

**Dr Kim:** The staging project will clarify stage IIIB. Other than the T4N0 or N1 patient that can be resected, the predominant stage IIIB classification patients are not going to be resectable because of bulky lymph nodes. Stage IIIB (N2) depends on the bulkiness of the lymph nodes. If it is a single nodal station, there are possibilities of resection. I would not say the patient is resectable up front, but it is possible that surgical resection could benefit the patient. Otherwise, for most of our patients with stage IIIA (N2) disease, surgery is not going to be a very good option. Past trials focused on stage IIIA (N2) patients that were deemed surgically operable up front before receiving neoadjuvant therapy. Therefore, it is a very subjective group of patients.

**JHASiM: What is emerging as the best alternative(s) for neoadjuvant chemotherapy in resectable stage IIIA NSCLC?**

**Dr Kim:** In the neoadjuvant chemotherapy sense, as opposed to the metastatic disease sense, we are looking for a response rate. We try to shrink the tumor to make our next line of intervention better, whether it be surgery or radiation. We then have to extrapolate because there’s no good data for stage III to tell one which is the best regimen to use as a neoadjuvant scheme. The highest response rate ever recorded in a phase III randomized trial in metastatic disease was approximately 32% with docetaxel and cisplatin.

**Dr Ettinger:** I don't think there's a difference in the effectiveness of the various chemotherapy regimens. Whether you use paclitaxel/cisplatin, paclitaxel/carboplatin, docetaxel/cisplatin, docetaxel/carboplatin or gemcitabine/carboplatin or gemcitabine/cisplatin, or even irinotecan/carboplatin or irinotecan with cisplatin, I think based on metastatic disease and based on the studies that have looked at these in the neoadjuvant setting, their effectiveness is about the same. I think the difference is not effectiveness in shrinking the tumor but in toxicity. Because you're not usually going to give more than 3 cycles of chemotherapy in a neoadjuvant setting, you're not going to be so worried about neurotoxicity. They're all associated with myelosuppression and degrees of thrombocytopenia. The only regimen that doesn't cause significant hair loss is gemcitabine/carboplatin.

If you're going to only use chemotherapy in a neoadjuvant setting, the more complicated question is whether you use chemotherapy alone to downstage the patient or do you use chemotherapy and radiation therapy together? Do you do it in a sequential fashion? Or, because we know that the concurrent is more effective than sequential, but has more toxicity, do we go in that direction (concurrently)?

When you add radiation, one problem is that there's usually only a 4- to 6-week window of opportunity to operate on the patient after chemoradiation. When the surgeon has to go in later, the combination of radiation and chemotherapy has caused fibrosis or other significant changes that make the surgeon's “landmarks” more difficult to assess and evaluate. The harder question to answer is should it be chemoradiation or chemo alone?

**Dr Brahmer:** I would agree. We have data on almost every chemotherapy combination, and most likely they are very similar. There's no one best regimen. It depends on which toxicities you want to avoid in a patient when picking a neoadjuvant therapy strategy. However, for patients with N2 disease, intuitively one would think that using combination chemotherapy and radiation therapy would provide a better chance of completely eradicating the tumor from the
lymph node, at least hopefully. Depending on the patient, that's how you choose whether you're going to use neoadjuvant therapy or combination chemotherapy and radiation therapy.

Dr Ettinger: The other issue is how much disease the patient has that's N2. Because when you give chemotherapy up front, chemoradiation (after the completion of the induction), or neoadjuvant therapy, you want the lymph nodes to be normal in the mediastinum, and you'd like to have some shrinkage of the primary disease. If the patient has minimal disease (no bulky disease), has had a mediastinoscopy, and the nodes are positive based on that, but the CT scan is essentially normal in the mediastinum, then you may want to do chemotherapy alone and then do the surgery with the hope that the chemotherapy will work and shrink the tumor and get rid of the micrometastatic disease.

If the patient has bulky disease that you may think is marginally resectable going in initially, then you may use chemoradiation in some fashion, as it may be more effective in getting good local control. In addition, you're assuming you will get rid of the micrometastatic disease with chemotherapy after in the adjuvant setting or with concurrent radiation in the neoadjuvant setting, if you're going to use a regimen such as in the RTOG study with etoposide plus cisplatin. Those are the factors. It's not just so much stage III; it's stage III what? Is it bulky disease, microscopic disease? Also, it is what you think the patient can tolerate.

JHAS/M: Does the level of difficulty in restaging patients with stage IIIA (N2) after neoadjuvant chemotherapy change significantly as a function of the type of therapy that the patient receives?

Dr Brahmer: It is more difficult to restage if the patient has received radiation therapy, especially when it comes to the role of PET after receiving neoadjuvant therapy or doing another mediastinoscopy. The other alternative is doing another bronchoscopy and biopsying those N2 lymph nodes. I think restaging is more problematic when you've received neoadjuvant radiation therapy rather than only chemotherapy.

Dr Ettinger: Yes, Dr Brahmer is absolutely right. With the use of the PET scan in staging and restaging, radiation causes inflammation, the PET scan would light up, then the question is are you dealing with persistent disease (if you did it in a neoadjuvant setting)? Or, are you dealing with inflammation? It's difficult to do a mediastinoscopy if you've done one before and you have a radiation field to contend with.

The surgeons usually do not like to go in to do a mediastinoscopy in that situation. Do you err on the side of inflammation, or do you wait a little longer? I think we're on a learning curve. Depending on the form of neoadjuvant therapy given up front, most of us end up giving post-treatment chemotherapy and delay further assessment, unless you're restaging to consider surgery as part of the therapy. It's easier going in if it's unresectable, in a sense, because then you can still proceed with chemotherapy. However, if you're restaging with the purpose of doing surgery, tissue becomes the issue.

Dr Kim: When we talk about restaging a patient after he/she has received neoadjuvant chemotherapy, whether he/she receives a platinum or nonplatinum agent, it doesn't really matter. It depends mostly on the patient's response. If they do have lymph nodes present, and he/she responds to the chemotherapy, it would be very difficult to restage that patient because their disease burden would be very minimal at that point.

There was a surgical report that a colleague shared with me that stated 30% of mediastinoscopies do not yield lymph tissue. It is unclear whether that is operator error, the wrong target, or because this is not after neoadjuvant. Mediastinoscopies, and doing full mediastinal staging, are not simple and straightforward processes. There's also variation with each surgeon in how he/she perceives an adequate lymph node dissection. Some surgeons just do sampling, whereas others do a full nodal dissection. That's a difference of sampling a few lymph nodes to almost 20 lymph nodes.

Therefore, the restaging aspect is difficult from a tissue or biopsy standpoint, especially if there's response, and especially if there's already inherent technical error. As for nonsurgical approaches of restaging, there can be PET scans done before and after neoadjuvant therapy. However, in my mind, a PET scan that has cleared is by far the gold standard. Depending on the type of surgery, you may reconsider the PET scan that has cleared is by far the gold standard.

JHAS/M: Is there a best approach for unresectable stage III NSCLC tumors?

Dr Brahmer: There are several approaches for unresectable stage III NSCLC, including induction chemotherapy followed by combined chemotherapy.
and radiation may not be the best strategy. I have started doing combined chemotherapy and radiation up front and using consolidation chemotherapy afterwards for unresectable stage III patients, based on trials from Southwest Oncology Group (SWOG).

Dr Ettinger: I think it first depends on whether the patient has stage IIIA or IIIB, and the “B” would be N3 disease, the contralateral nodes or supraclavicular nodes, not pleural effusion. It also depends on the symptoms. In general, approximately 10% to 15% of patients may be asymptomatic. However, if I have a patient with severe shortness of breath, secondary to bulky disease, I want to make sure I get shrinkage of the disease and a local control.

Thus, I agree with Dr Brahmer. In that situation, I usually start with combined chemoradiation. However, if the patient has minimal symptoms, and is still unresectable, I may go with systemic chemotherapy first with the idea of seeing if the chemotherapy is effective at shrinking it down, then go with the concurrent chemoradiation.

The Locally Advanced Multimodality Protocol study showed that concurrent chemoradiation up front was better than induction followed by concurrent. The reason was that more patients were able to get to chemotherapy with the concurrent when they started it first rather than the induction. Dr Brahmer said, the CALGB did a study comparing induction therapy followed by concurrent versus concurrent up front, and they couldn’t show an advantage to either one, which was somewhat disappointing.

Part of the problem is that there’s more toxicity with the concurrent therapy. You may as well get any toxicity done with early on rather than drag it on with regard to induction chemotherapy followed by concurrent chemoradiation therapy. I think, in part, it’s a function of the medical oncologist and the radiation oncologist treating the patient. Unfortunately, there’s a price one pays when going for a cure, even with unresectable disease. One has to be very aggressive, and the patient has to be a partner and willing to accept some toxicity with the hope that what we’re going for is a cure, even in stage III unresectable disease. Therefore, in my opinion, and that of many others, there’s no specific way to treat stage III unresectable disease, except as a combined-modality approach. That’s why there are multidisciplinary conferences to discuss these patients.

Dr Kim: My standard approach to unresectable stage III is concurrent chemoradiation up front. The radiation is pretty standard (fractions >60 Gy), and the chemotherapy I use is generally a cisplatin-based chemotherapy regimen with another agent. One of the more popular regimens lately has been using cisplatin and etoposide with radiation, followed by single-agent docetaxel. This is a result of the SWOG 9504 study, which yielded a 5-year survival rate of 29% in stage IIIB.

JHASiM: Many molecular and genomic techniques have become available recently for cancer diagnosis, staging, and determining the proteomics of lung cancer. How efficient has the bench-to-bedside process been?

Dr Brahmer: I think it’s been a mixed bag. There’s been some very quick translation of laboratory research and then others that take an extremely long time, but there are pluses and minuses to each. Certainly, funding can also be an issue, plus now we’re running into problems of having so many targeted therapies and options, and there’s only so many patients, thus trying to increase our accrual rate and patient participation in studies are also factors.

Dr Ettinger: There are several aspects to this. If you ask me have we made advances in regard to targeted therapies from the bench to the bedside, I would say yes. With some of the targeted therapies, (eg, epidermal growth factor receptor [EGFR]) I think we’ve raised more questions than we’ve answered. Now we have mutational analysis and everybody thought you had to have the EGFR mutation to have a response, but we now know that’s not entirely true, that you can have an increase in gene copy. You use a clinical assessment to treat a particular patient. If a Korean woman is a nonsmoker with adenocarcinoma, she has a good chance of responding to a small-molecule tyrosine kinase inhibitor. With regard to proteomics and identifying markers that predict for overall survival, there have been a lot of investigators over time, such as Dr Raphael Rosell in Barcelona and others. Many markers predict for whether the patient is going to do well. Yet, have they come into clinical practice? No. Have they been around a while? Yes. No one has really done the right study, the big study, to answer the question about using it in a predictive fashion.

Taking breast cancer as a good example, we look at estrogen receptor (ER), progesterone receptor (PR), and HER-2/neu, and yet they are used in conjunction
with the stage of the patient. Because, in essence, if the markers were as important in predicting survival rates, then it should be in the staging classification. What predicts prognosis and treatment is the TNM, not whether the patient is HER-2/neu positive or is, in breast cancer, ER/PR positive.

When people talk about proteomics and various markers, they’re talking about individualized therapy down the road. What most of us are trying to do, especially in advanced disease, is make lung cancer a chronic disease. We’ve come a long way in a sense, such as breast cancer, colon cancer, and prostate cancer, and I think there are major advances, but we have a long way to go.

Dr. Kim: Our molecular and genomic techniques have very much diversified from 5 years ago, especially in lung cancer. However, the practical application of any of these techniques into the clinic for the patient has been less than ideal. The work stemming from EGFR, and a mutational or amplification status, has certainly made its way into clinical research, and we will be testing the populations of patients to see if they are the ones that deservedly should be treated with this class of drugs. However, it doesn’t mean we would exclude other patients who didn’t have these characteristics from being treated with these drugs such as erlotinib. Cetuximab is another drug that would be very interesting to test with radiation, based on the head and neck experience with stage III. Bevacizumab is the first drug to show a survival advantage when combined with chemotherapy in stage IV, thus it makes sense to also test that drug in stage III. Perhaps it has radiosensitizing properties by itself, but certainly it may make chemotherapy more potent with fewer side effects. Other drugs with promise include ZD6474, a combined VEGF/EGFR drug, and other VEGF drugs, such as sorafenib, which was recently approved for metastatic renal cell carcinoma.

What is pushing lung cancer research right now is we want to predict who is going to respond or do well with certain therapies. Examples are tamoxifen and breast cancer, in addition to trastuzumab. Unfortunately, in lung cancer we have not identified a marker that predicts survival. The mutation or the amplification with EGFR is being tested, but we don’t have any survival data. Hopefully, that will be answered through some of the cooperative group trials. With VEGFR, it’s even more of a question how to predict who deserves to be on bevacizumab long term, as there are also economic implications. The drug is effective in lung cancer, thus it is important for patients.

Lung cancer is a dynamic field right now. There are many more drugs available for patients. Patients are living longer with lung cancer. We now have many oncologists with more experiences of patients living beyond 1 year, even 2 years, because there are different therapies. We have learned that with combination chemotherapy we want to treat patients who have good performance.
status and without a lot of comorbidities, per se. If they can tolerate this type of therapy, it usually leads to better outcome. When patients have to use single-agent therapy it usually means they cannot tolerate doublet therapy, thus these patients automatically fall into a worse prognostic group. With the EGFR therapies, some patients may not need combination chemotherapy, especially front line. Perhaps some patients, especially the Asian or nonsmoking patients, may benefit from single-agent therapy with a drug such as gefitinib or erlotinib, which is approved in the United States, or even biologic combination therapy such as bevacizumab with erlotinib. This boils down to finding those patients who have the right profile for the right type of therapy. In stage III, it is utterly important to obtain tissue, and perhaps then we can figure out which agents should be used with radiation in stage III, or combined-modality therapy, or even which agents should be administered as a neoadjuvant approach before surgery. The central focus is that we need to get at tissue to help sort out which patients will do best with certain therapies, based on their pathology or predicted response.

**JHASPark** What are the most daunting challenges that remain in how to choose a multimodality approach for stage III NSCLC? What will treatment be like 5 to 10 years from now?

**Dr Brahmer:** I think some of the biggest challenges in the next several years will be trying to find regimens or combinations that patients can tolerate, decreasing the toxicity in addition to improving how they work, and being able to take what we learn and apply it to most, if not all, of our patients, particularly patients that are more fragile and who may not be able to tolerate our current combination therapies. I think 10 years from now we won’t be doing the same thing. Hopefully, we’ll have moved on and be able to tailor the combination of therapies to each patient, their comorbidities, and their tumor characteristics.

**Dr Ettinger:** I’m encouraged because I think what’s going to happen in 5 to 10 years from now is that we’re going to have fewer and fewer patients with stage III and IV disease. We’re going to have major advances in screening and early detection, and Dr. Brahmer is working on this. Smoking has decreased in the adult population, especially in males. Ten years from now it should be down even further. I think our therapies are getting better, thus even advanced disease will become a chronic disease. Even now, we’re curing more patients with stage III disease. We’re going to have many more things in the way of therapies—targeted therapy, chemotherapy, and probably systemic radiation therapy, as another armamentarium to use.

An even bigger problem that we face 10 years from now is who is going to pay for all of this? This is pretty expensive, and I don’t think we have a clue as to what this will cost the healthcare industry. We have a hint of this with what the combinations of targeted therapy, chemotherapy, and radiation are costing patients now. If we don’t solve that problem, you may have all these great therapies and only a select group of patients will get them.

**Dr Kim:** The most daunting challenge in how to choose a multimodality approach for stage III requires the treating physicians to work as a team. That includes the surgeon, the radiologist, the radiation oncologist, and the medical oncologist. The opinions need to be gathered using imaging, in addition to the pathological staging, and that will help direct which patients are most appropriate for a predominantly surgical or a predominantly radiation-based approach. The chemotherapy is usually included as a complementary, rather than a predominant, approach for these patients.

The future will hinge on better radiology techniques. Maybe there will be better accuracy with tests, such as PET scanning, and better surgical techniques and easier ways to sample lymph nodes. There may be a way to predict which lymph nodes need to be done, analogous to sentinel lymph node biopsies in breast cancer or melanoma. Maybe chemotherapy will be used less as some of these biologic agents are tested and prove to be just as efficacious without the chemotherapy. If that can be done, then side effects will be reduced. That will be one of the major changes.

The other major change will be whether consolidation chemotherapy benefits the patient. It’s been very promising, especially with 3 cycles of docetaxel. In the SWOG 9504 phase II study, patients lived much longer and this is being verified now with a larger phase III study. Therefore, for treating the unresectable population, that’s the main question that needs to be answered. In the resectable population, it’s the requirement of the entire team to make that decision.