INTERVIEW

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Melanoma Management

A melanoma odyssey – a conversation with Vernon Sondak about a career in melanoma treatment and research

VERNON SONDAK* SPEAKS TO LAURA MCGUINNESS, MANAGING COMMISSIONING EDITOR

Vernon Sondak is Chair of the Department of Cutaneous Oncology and Director of Surgical Education at the H Lee Moffitt Cancer Center and Research Institute in Tampa, FL, USA. He is also a Professor in the Departments of Oncologic Sciences and Surgery at the University of South Florida Morsani College of Medicine. His research interests include the surgical treatment of malignant melanoma in adults and children; the surgical treatment of Merkel

cell carcinoma, desmoid tumors and cutaneous soft-tissue sarcomas, including dermatofibrosarcoma protuberans; the adjuvant therapy of melanoma; and the evaluation of new therapies for patients with localized or disseminated melanoma. Sondak has also been a leader in studies of the surgical treatment of melanoma and other cutaneous malignancies, particularly in the application of sentinel lymph node biopsy to the staging of melanoma and Merkel cell carcinoma. He is actively involved in ongoing analyses in order to determine which patients with thin melanomas are most likely to benefit from sentinel node biopsy, as well as which patients with sentinel node metastases are most likely to have further metastases identified in other regional lymph nodes. Sondak is the author or coauthor of over 300 articles in peer-reviewed publications, 165 abstracts, eight books and 67 book chapters.

Q How did your career lead you to the Moffitt Cancer Center?

I spent over 16 years at the University of Michigan (MI, USA), where I was heavily involved with the Multidisciplinary Melanoma Clinic. I really enjoyed my time there; I loved the people I was working with and the system they had set up there. But at the end of the day in the multidisciplinary clinic, everyone went back to their own department with their own leadership to report to. Sometimes, that meant we were torn in different directions. The Moffitt Cancer Center (FL, USA)

attracted me because of its truly programmatic orientation. The Department of Cutaneous Oncology is made up of all of those people who deal with melanoma and other cutaneous malignancies, and so it is never a matter of saying “What do they want to do in the other departments?” Rather, it is a matter of saying, “What do *we* want to do as a unified group?” We control our own resources in terms of clinical trials personnel and deciding which trials to do and which not to do. We truly have our own team, which makes all aspects of care better for melanoma patients and

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Interview

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physicians alike. There is no 'us against them', because it is only us. I do not want to make it too dramatic or imply that this is a huge problem in other places, but Moffitt is the only place in the USA that has this unique academic and administrative organization, where all of the people involved with treating melanoma patients are in the same department. The ability to be in that environment and to lead that group was what drew me to Moffitt. I saw the potential that Moffitt's approach had to be the most ideal way to take care of melanoma patients and to make real progress on the research side of things.

I think the other aspect that is different about Moffitt compared with a more typical university environment is, while there is a lot of research going on at both types of institutions, at Moffitt the researchers are so focused on conducting research that will directly improve patient care. It makes it easy to work with laboratory researchers because they are actively looking for clinical applications and connections between what they are doing in the laboratory and what we are doing with patients.

Q What was it that drew you to the field of melanoma?

It started early on, first when I was in medical school and then in surgical training. I had some great mentors, particularly Peter Mozden, who was the Chief of Surgical Oncology at Boston University (MA, USA) while I was a medical student there, and also another surgical oncologist, Peter Deckers, who went on to be the Dean at the University of Connecticut Medical School (CT, USA). Those two individuals in particular were very influential when I was a medical student, and steered me towards surgical oncology as a career. I then went to the University of California, Los Angeles (UCLA; CA, USA) where Donald Morton was the Chief of Surgical Oncology and obviously one of the giants in the field of melanoma.

Very quickly, I was attracted to what was going on in the melanoma field. I was quite interested in other soft-tissue tumors as well, but what I liked about melanoma was the ability to take care of every part of the body. I was operating on feet, lymph nodes, legs, arms and heads; there were no anatomic limitations, as melanoma can involve every area and organ of the body. Over the years, melanoma has been this huge riddle: a conundrum where, on the one hand, it can be picked up early on the

skin, and if you find it as a thin lesion, you can obtain a cure rate of close to 100%. On the other hand, however, with a few more millimeters or a few cells in a lymph node, suddenly it goes from being nearly 100% curable to one of the most aggressive and refractory malignancies that human beings can ever suffer from. But, paradoxically, you can also have a patient with widespread metastatic disease where the disease regresses entirely on its own, without any treatment. I saw one patient whose tumor just went away by itself after a severe infection. So in practice, you see the great curability of melanoma if it is found early, but also the refractory nature of the cancer in some patients, and then there are people with very advanced disease that you can still help. It is such a compelling field to get into, both as a surgeon and as a researcher. Of course, the last few years have been filled with tremendous excitement and achievement, which has been extraordinarily gratifying.

There is another personal side to the story, and I did not even know this until after I had made the decision to specialize in melanoma. I learned while I was still in my surgical residency that my grandmother, who I had always thought had died of a brain tumor, had in fact died of a brain metastasis from melanoma. So it turned out that I had a strong family connection with melanoma, a personal connection that I did not actually know existed beforehand.

Looking back on when I began in this field (I graduated from medical school in 1980 and that was when I started as an intern at UCLA), melanoma was not nearly as well-known as it is today. That was true for doctors, patients and lay people. So at the time, it was an attractive area that not many people were studying, and that certainly drew me to the field of melanoma as well.

Q What would you cite as your biggest professional achievement to date?

Well, I am not absolutely sure I am the one to judge what my biggest achievement has been, but I hope I have made a few contributions to surgical oncology over the years. I would say that one of the things I am most proud of is the cadre of people who I call my 'professional family', including my fellows and residents who I have trained and worked with during my time at the University of Michigan and at the Moffitt Cancer Center. These individuals have gone on to do so many great things. I was

able to work with terrific residents in Michigan who are now in leadership positions all over the USA. Similarly, in the decade that I have been in Tampa, my fellows have gone on to have great success in their careers. When I think of my professional family, it is not just the trainees I think of; I am also proud of the success that the faculty members of the Department of Cutaneous Oncology at Moffitt have gone on to achieve, not just surgeons, but medical oncologists, dermatologists and pathologists as well who have gone on to be successful, and we have been successful together as a department. That is a big professional achievement for me. It culminated just recently when Moffitt was awarded a Specialized Programs of Research Excellence (SPORE) grant for our work in melanoma and other forms of skin cancer. That is a huge achievement as there are only a few centers in the USA that are awarded this grant, and I see that as objective evidence that what we are doing, both clinically and in research, is respected at the highest level. It is not my SPORE grant; I am not the principal investigator. It truly is a Moffitt collaborative effort, and I am very proud to have been in the position to support that kind of achievement.

But as proud as I am of the SPORE grant, I am at least as proud of one of our junior faculty surgeons who just got his first NIH grant, a K23 Career Development Award from the National Cancer Institute. I think this is further evidence that this multidisciplinary approach – this true team approach we have here at Moffitt – is effective both for patients and the physicians and staff.

Q Over the years, you have been quite closely involved with the Southwest Oncology Group (SWOG) – what have you learned from this?

Much of what I have learned goes back to what I have been talking about before, namely how important it is that melanoma care should be a multidisciplinary effort. What I learned with SWOG was how important every member of that multidisciplinary team was to making progress and giving patients the best outcome. More importantly, I learned how to use a multidisciplinary research organization to make progress in patient care. SWOG gave me training and a level of familiarity with clinical trials research, and taught me how to frame questions about clinical problems in a way that research studies could answer. It is important in a cooperative group

to look for issues that broadly affect everybody who is taking care of a melanoma patient. You try to look beyond your own specialized niche, trying to answer questions that could assist people who are taking care of melanoma nationally and even globally.

Through SWOG, I have been involved in many trials with adjuvant therapy, including those that helped establish the role of adjuvant interferon. It is a controversial treatment and still has its share of negative aspects, but it set the bar for adjuvant treatment. We said, “Here’s what can be done with interferon.” Ever since interferon was approved in 1995, the cooperative groups have been trying to do better, and now I think we are on the verge of surpassing adjuvant interferon, perhaps with ipilimumab. However, I am even more excited about anti-PD1 treatments as possible adjuvant therapies. I think we are poised to make real progress, and it will be built upon the foundation of all of those studies of adjuvant interferon, pegylated interferon and vaccines that we completed in the cooperative group setting. I am hoping that adjuvant therapy will be transformed by the new drugs that are coming along, and if so, we will largely have the cooperative groups in the USA and around the world to thank for that. During these cooperative group studies, I have had the pleasure of working closely with so many terrific people all across the world, which has been the icing on the cake, so to speak.

Q What are the most exciting trials that you think you have been involved with?

I feel like the most exciting ones are yet to come. It has been amazing to be involved with trials involving BRAF inhibitors, to see patients who are in terrible shape, who are suffering significant side effects and symptoms from their cancer with obvious, visible, large tumors, and then a week or two later they say “I feel a lot better and I can tell these tumors are already getting smaller.” That is something we just never saw before. Even with immunotherapies such as IL-2 and ipilimumab, although we knew we were making a difference in some patients, it was not this dramatic shrinkage that you can see with the targeted therapies.

On the other hand, of course, those dramatic and rapid improvements are sometimes associated with just as dramatic and rapid failures. A large part of our SPORE grant is to look at why people fail on these BRAF inhibitors, why the

targeted therapy stops working and what we can do in order to delay or prevent that resistance from emerging. We hope to change the paradigm of how we think of melanoma from one that is a rapidly fatal disease to one that we have a chance to control in the long term and even cure in a number of patients. I think that the opportunity to make such a difference for patients with metastatic melanoma with new drugs is clearly the most exciting thing that has happened in melanoma and in the clinical trials that I have had the privilege to have at least some involvement with.

Q You were a founding member of the International Sentinel Node Society, how have you seen our understanding of cancer & the lymphatic system progress?

I am particularly interested in this area, and of course I owe a huge debt to my mentor, Donald Morton, who was the pioneer of sentinel node biopsy. Through that technique, he changed the way we think about lymph node metastases. I remember as a resident working with Morton to try to identify the sentinel node in a melanoma patient, and thinking, “I don’t understand this idea, why would we care about one lymph node? Either take them all out or don’t take any of them out. Why would taking one lymph node out be better than taking all of the lymph nodes out?” Obviously, time proved me wrong, showing that it was indeed important to find that one sentinel node. We learned that we could dramatically improve our understanding of melanoma prognosis and take some of the mystery out of this disease. Through a sentinel node biopsy, we can now take two patients whose melanomas look identical but where one has a metastasis to the lymph node, and say that the chances are pretty high that the one with the metastasis in the lymph node will do worse than the one without the metastasis. That was a transformational observation, and now we can spend our time figuring out why these two melanomas look identical on the skin, yet only one has been able to metastasize. Is it something deficient in the patient’s immune response? Is it something bad about the tumor? Is it something unique about the lymph node? Just being able to ask the question that way and compare two otherwise-identical patients has led to leaps in our understanding of melanoma and how it metastasizes. It has taken away one of the many veils that melanoma hides behind and made the disease just a little bit more transparent. So many times

we were mystified by a melanoma that behaved in a way that we did not expect, but in retrospect, it was because we did not fundamentally understand where the lymph nodes draining the melanoma were and whether they were clean or whether they had micrometastases in them.

Q The thickness of a melanoma & whether thin melanomas justify sentinel node biopsy is a hot topic at present. What are your thoughts on this?

I think it is one of the hot topics in surgical oncology today. Two years ago, joint American Society of Clinical Oncology (ASCO) and Society of Surgical Oncology (SSO) evidence-based guidelines came out regarding sentinel lymph node biopsy in melanoma. They concluded that we still could not tell what to do about the thin melanomas, because there were not enough data. Neither the MSLT-1 trial (the landmark randomized trial of sentinel node biopsy that Morton conducted), nor the Sunbelt Melanoma Trial, which have proven so crucial to our evidence base for recommending sentinel node biopsy for intermediate and thick melanomas, addressed the issue of thinner lesions. We have almost no prospective trial data, and certainly no randomized trial data, about thin melanomas and sentinel node biopsy.

Why does that matter? Right now, most newly diagnosed melanomas fall into the category of 1 mm or thinner. So we have a large number of patients and only a relatively small number of those are going to die from melanoma. Yet because it is the largest group of patients today, even if only a few of them die on a percentage basis, this means that a lot of the melanoma-related deaths that will occur going forward will come from this group of otherwise lower-risk individuals. This is why distinguishing the few high-risk individuals in that population could be extremely rewarding. There are a large number of people you can reassure and say, “It looks really favorable for you.” To a smaller number of patients, you can say, “OK, it looked favorable, but there’s already a problem in the lymph node. If we intervene now, maybe we can have a major impact.” I do believe that it is possible to intervene and make an impact for thin melanoma patients with nodal metastasis.

Balanced against that is the cost in economic terms and in individual patient morbidity. Finding the right balance is a challenge. It is clear that if we conducted a sentinel node biopsy in

everyone with a melanoma, no matter how thin, we would be wasting a lot of resources, causing morbidity and not helping most of these patients. Yet I am convinced that at least some patients with thin melanomas should have a sentinel node biopsy, and my personal feeling is that this is an area where personalized, ‘precision’ medicine is absolutely what we should be practicing. We should be looking at every single patient with a thin melanoma as an individual, and utilizing as much information as we can in making the final decision about sentinel node biopsy. Right now, the specific genes in thin melanomas that influence the risk for early nodal metastasis are not understood, but someday I believe they will be. Today, it is the thickness, the mitotic rate, the patient’s age and their general state of health that are all factors that we can combine with the patient’s preferences in making our final decision. What is the patient most concerned about, what does the patient want to get from their treatment, how proactive do they want to be and how aggressive do they want to be? All of those things need to be synthesized, and I think there are few places in medicine where there is a more truly individualized decision-making process compared with deciding about thin melanomas and sentinel node biopsy.

Q With melanoma being such a developing & fast-paced field, how do you think clinical investigators & basic researchers can best communicate & collaborate in order to make effective global advances in the management of melanoma?

Over the last decade, I have been honored and excited to be involved with two important new groups that have aided this effort, namely the Society for Melanoma Research (SMR) and the international group of Melanoma Centers, each of which holds an annual meeting relating to melanoma research and treatment. These two organizations have been important driving forces in helping to propagate the changes in melanoma that we have seen at the clinical level.

The SMR is illustrative of what has happened in melanoma over the last decade. I remember when it got started in 2003 – it was a small organization with relatively few people studying the basic biology of melanoma. There was a lot of uncertainty – some would even say pessimism – about whether we were going to be able to crack this difficult tumor or whether melanoma would always somehow be one step

ahead of us. Fast forward to the 10-year anniversary meeting of the society in November 2013, which was held in Philadelphia (PA, USA), the same city where the first meeting was held in 2003, and the atmosphere was totally different. It was now a very large, vibrant society, with clinicians and researchers together, and with many people there studying the basic biology of melanoma. A great deal of emphasis was placed on understanding both the immune system and the genetics of the tumors, and even how they interact. There was a feeling that we were winning this battle, and that the research we were doing was directly contributing to improved outcomes for patients. It has been extremely gratifying to see this society grow in importance and gain so much momentum.

The meetings of the international group of Melanoma Centers have also been very gratifying. When I go to these meetings, I meet people from Australia, the USA and northern Europe, of course, but I am also meeting people from those countries that we do not think about as having major melanoma epidemics, such as China, Greece and Brazil, yet they are all eagerly embracing the new advances and working in multidisciplinary teams. This idea of multidisciplinary care has spread across the entire globe and has now permeated into even the smallest countries – it really has taken root. That organization of Melanoma Centers, which started from a dinnertime conversation among half a dozen people, has grown into a major international force for the clinical management of patients with melanoma. The last 10 years have demonstrated this, and people are voting with their feet – they are coming to these melanoma meetings and they are working in teams, seeing the success of this approach and that it is self-sustaining. We have created something that is growing and sustaining itself, and that is extremely gratifying to be a part of. Still, for all of our progress, we are still looking for new and better ways to communicate the advances that are being made to all of the people who are interested in melanoma. This is still a challenge, as there is no single place where you can always go and find out all of the latest information and what is being done in melanoma. Things are changing so rapidly that it is tough to keep up. People who were my fellows and have been out of the field for a year or two are calling me up and they are saying, “People here at my place are asking about the latest news regarding BRAF

inhibitors, ipilimumab, sentinel node biopsy, genomics and pediatric melanoma. How do I stay informed about this? How do I stay as cutting edge as you are?" Even I am not always as cutting edge as I need to be; I also have to rely on my colleagues in order to get the latest news. This is a challenge facing us as a field. When melanoma was a tumor type that few people were very interested in and progress was hard to come by, it was not such a big deal. Now that it is front and center of research, the poster child for targeted therapy and advances in immunotherapy, and a place where surgical advances are being made, I think we have to do a better job of this. Those two organizations that meet every year are a big part of getting the word out, but we clearly have opportunities to do better, and doing so would be a real sign of the maturation of our field. When we have better ways of communicating what we have achieved so that all of the people who are interested in melanoma can find out the latest news, then this will be a sign that we have reached where we need to be.

Q What is your current research focusing on?

The one area that I hold dearest to my heart right now is the management of melanoma and related skin neoplasms in children. Here in Tampa, I see approximately one new case every month in a patient under 18 years of age with either melanoma or an atypical Spitz nevus, or something similar. You not only have the trauma of a child, perhaps as young as 4 years old, being diagnosed with a potentially lethal condition, but you are superimposing huge degrees of uncertainty on that as well. We are often not even sure that we are looking at cancer versus a benign tumor, because the pathologists cannot determine this with certainty or are disagreeing among themselves. Of course, this can be extremely frustrating for the families and even the patients, if they are old enough to understand. This diagnostic uncertainty creates an even greater degree of anxiety than the situation would normally engender. I am personally very interested in what we can learn about melanoma and atypical melanocytic lesions in children and how we should treat these lesions. My approach is to be relatively aggressive. Here, we are really focused on balancing the risks and the benefits. Are we overtreating some children? Undoubtedly we are, just as we are probably overtreating some adults with melanoma. Yet I am personally very confident that we are going to make more progress, and

we are going to understand these tumors in children better in the future than we do today. Unfortunately, I have treated children with melanoma who go on to die from the disease. Sometimes it has taken years and sometimes it has taken over a decade, but I have seen enough to know that just because they do well for a few months or a couple of years, this is not enough to say that it is not a dangerous situation.

Q What is next for you?

Here at Moffitt, we are in the process of building a new clinic building that will house our entire outpatient melanoma effort, including our outpatient surgeries, our imaging facilities and our infusion center. We hope that we will also eventually move our key melanoma researchers as well. We are about 1 year away from opening this building. We have used the wonderful Melanoma Institute Australia as a model. I am not sure that simply by erecting a building here in Tampa we can have quite as much impact as they have had in Sydney, but that is what we are looking to as our ultimate goal. This is obviously not the only thing we are working on, but it is a big thing on our radar right now.

Dedication

Shortly after this interview was conducted, the melanoma community learned of the passing of one of the true giants in the field, Donald L Morton (1934–2014). In recognition of the enormous role Morton played as a mentor and supporter throughout his career, Dr Sondak has asked that this published interview be dedicated to his memory.

Disclaimer

The opinions expressed in this interview are those of the interviewee and do not necessarily reflect the views of Future Medicine Ltd.

Financial & competing interests disclosure

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