Surgical Considerations Following Induction Therapy for Stage IIIA Disease

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Seeking new solutions through the windows of opportunity offered by induction therapy for locoregional disease. The predominant model of care for locally advanced solid organ malignancies involves a shotgun approach. Indeed, the full range of "omic" strategies are currently insufficiently exploited when assigning treatment regimens to patients with IIIA non-small cell lung cancer (NSCLC). Despite the advent of precision oncology, management strategies for stage IIIA NSCLC remain relatively untapped despite such successes as those described in the PACIFIC trial [1]. Indeed, the workhorses of curative intent therapy for IIIA NSCLC and their various permutations (surgery, radiation and chemotherapy) remain essentially unchanged over the last 25 years since the first trials of induction chemotherapy were performed in the early 1990s [2-3]. The paradigm of multimodality therapy combining local and systemic treatments holds true today and offers the best available oncological outcomes recorded to date. After decades of debate, emerging data seem to conclude that induction therapy with chemotherapy alone or concurrent chemoradiation offer essentially identical results when planned prior to surgery [4]. However, these data remain largely retrospective with few randomized head to head comparisons in this most heterogeneous of stage groupings. Hence, not only has stage IIIA remained a highly heterogeneous cohort with a wide spectrum of disease burden, but its relative rarity has hampered the execution of innovative randomized trials. Thus, most centers have adopted a preferred institutional approach based on expert readings of the available literature. These variations in care have led to heated debates over what is essentially a game of musical chairs, arranging various permutations of conventional therapeutics for which the outcomes are largely identical. In this respect, the old debate of whether to give induction chemotherapy or concurrent chemoradiation misses the point and overlooks a tremendous opportunity for discovery. Years of clinical trials have taught us that approximately 15 to 20% of patients will experience a major pathological response after induction chemotherapy [5] and approximately one third will have a pathological complete response after concurrent chemoradiation [6]. Yet, we are no closer to selecting those patients most likely to benefit most from these conventional therapeutics. The windows of opportunity offered by induction therapy in surgically resectable IIIA NSCLC are numerous and vastly powerful. Properly exploited, these opportunities make IIIA NSCLC the perfect pivot point for discovery that will inform both the metastatic setting and novel approaches to early stage disease. As NSCLC patients are offered more therapeutic options, the ability to tailor induction therapeutics based on predictive analyses up-front remains under-exploited in IIIA disease. Current trials exploring the value of checkpoint inhibition prior to surgical resection for locally advanced NSCLC assign patients randomly to the available combinations. This again is a key moment to provide improved selection through the extensive correlative science pipelines offered by these window of opportunity trials [7]. The surrogate measure of major pathological response and its close association with long term survival outcomes provides a powerful incentive to rapidly adopt new regimens into the corpus of available therapeutic options. Our program capitalizes on the availability of large tissue samples offered by patients treated with multimodality therapy in surgically resectable IIIA NSCLC, to establish lab-based patient avatars. These living and highly personalized biobanks provide the necessary materials to profile and generate a lab-proven first line therapeutic regimen. While such programs would be highly inefficient in early stage disease where cure rates are much higher, patients with stage IIIA have high rates of recurrence and generally benefit from a sufficiently long disease-free interval. This luxury of time offers yet another window of opportunity where patient-derived xenograft models and organoids are generated from the surgical specimen to create the necessary patient avatar to execute a predictive analysis and establish the optimal next step for the significant number of patients who will experience progressive disease. Moreover, the sensitivity of liquid biopsy protocols is easily tested in this setting where a significant proportion of patients are placed into remission with no radiological evidence of disease [8]. Such opportunities provide the ideal setting to revisit our surveillance strategies which have become so resource intensive, yet offering so little measurable benefit [9]. Finally, a dedicated research program centred on locally advanced NSCLC provides a desirable clinical entity to rapidly establish predictors of response and failure to conventional and emerging biologicals by leveraging all "omic" platforms, from clinical to radiological and from pathological to deep sequencing, metabolomics, immunoprofiles and beyond. Such research provides the pipeline to generate the true essence of personalized medicine in NSCLC, which can easily be translated to both early and late stage disease. References: Antonia SJ, et al. 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Small Lung Tumours: High Risk Lesions and Contraindications to Stereotactic Ablative Body Radiotherapy (SABR)

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The development of SABR has revolutionised the non-surgical treatment of small, node negative lung tumours, both primary and metastatic. SABR is a convenient, painless, inexpensive outpatient procedure and there is now randomized evidence that it not only results in better local control than conventionally fractionated radiotherapy in patients with inoperable peripheral stage I non-small cell lung cancer, but increases survival as well. The impressive local control rates of over 80% have tempted some investigators to expand the indications for high dose hypofractionated SABR beyond small peripheral tumours. Perhaps the most controversial extended indication is the use of SABR for "central" lung tumours. There is no agreed definition of what constitutes a central tumour, although in the absence of consensus, the "no-fly zone" described by Timmerman is widely used even though it was based on a very small number of events. Phase II trials have been interpreted as indicating that SABR of central tumors has acceptable toxicity (RTOG 0813), even though there was a 3% mortality likely resulting from