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Andrés Cervantes

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Department of Medical Oncology, Biomedical Research Institute INCLIVA, CiberOnc, University of Valencia, Valencia, Spain

Correspondence to
Professor Andrés Cervantes; andres.cervantes@uv.es

SHORT-COURSE RADIOTHERAPY FOLLOWED BY DELAYED SURGERY BECOMES A VALIDATED ALTERNATIVE TO TREAT INTERMEDIATE-RISK LOCALISED RECTAL CANCER

The full publication in *Lancet Oncology* of the Stockholm III trial helps us to understand that short-course radiotherapy in patients with localised rectal cancer could also be followed by delayed surgery.[1] During more than 14 years, more than 800 patients with rectal cancer not showing unresectable features were randomised in a two-arm versus three-arm study with a non-inferiority design. Patients could be randomised to short-course radiotherapy (5×5 Gy) and immediate (within a week) versus delayed (4–8 weeks) surgery. In the three-arm randomisation patients could also be allocated to a long course of concurrent chemoradiation (25×2 Gy), with surgery performed 6–8 weeks thereafter. Time to local recurrence was established as the primary endpoint. Interestingly, short-course radiotherapy followed by delayed surgery was proven to have less acute toxicity and a lower postoperative complication rate compared with immediate surgery. Oncological results were similar among the three arms. The authors conclude that short-course radiotherapy with surgery delayed for 4–8 weeks might have certain advantages over immediate surgery in rectal cancer treatment. Another interesting fact observed in this study is that tumour regression and downstaging is seen in the delayed surgery arm, achieving a pathological complete response rate of 11.8%, while tumour regression is rarely appreciated in the immediate surgery group.[2] Moreover, delayed surgery allows the integration of chemotherapy after short-course radiation in patients with locally advanced tumours. This strategy has been further developed in the RAPIDO trial, which already completed accrual and whose results are to be reported in about 3 years from now.

A COMPREHENSIVE MOLECULAR CHARACTERISATION OF UTERINE CARCINOSARCOMAS REVEALS PATHWAYS TO HELP IN DEVELOPING A BETTER ORIENTED PERSONALISED APPROACH

Uterine carcinosarcomas are uncommon malignancies involving 5% of all endometrial neoplasms. Mixed morphological features with epithelial and mesenchymal components characterise them. In general, they are treated in a way similar to high-grade serous endometrial or ovarian malignancies, but its molecular landscape was far from being known. A paper published in *Cancer Cell* by the Cancer Genome Atlas Research Network reveals the most common molecular alterations harboured by them.[3] In a very comprehensive analysis, including genomic, epigenomic, transcriptomic and proteomic characterisations of a series of 57 uterine carcinosarcomas, the authors show extensive copy number alterations as well as a high frequency of mutations. The most relevant were found in TP53, PTEN, PIK3CA, PPP2R1A, FBXW7 and KRAS. This observation makes them very similar to high-grade serous tumours. Recurring focal amplifications include those containing the oncogenes *TERC, FGFR3, MYC, KAT6A, MDM2, ERBB2, CCNE1* and *BCL2L1*. Recurring focal deletions contained the tumour suppressors *PTPRD* and *RB1*. These multiple molecular alterations may add some experimental therapeutic options, such as the use of PARP, EZH2, cell-cycle and PI3K pathway inhibitors. But perhaps the most striking feature found was the strong epithelial mesenchymal transition signature in the transcriptomic analysis. The significant association of epithelial mesenchymal transition scores extends to the expression of E-cadherin at the gene and protein levels, as well as to *CDH1* regulators *SNAI1/2* and *ZEB1/2*, which are direct miR-200 family targets. The expression of 131 genes identified as being correlated with epithelial mesenchymal transition was more strongly correlated with the epithelial mesenchymal transition scores in uterine carcinosarcoma than in other gynaecological cancers. All these findings are expected to contribute to the development of a more rational and personalised approach to the treatment of this uncommon uterine neoplasm.

JAKSTAT3 SIGNALLING AXIS IS ACTIVATED IN LUNG CANCER AND BECOMES A POTENTIAL TARGET FOR TREATMENT

Better and more precise knowledge is needed to unveil the mechanisms of tumour progression and metastases in lung cancer. In this

regard, investigators at Stanford University have recently published in *Nature Medicine* a series of elegant experiments showing the potential value of the Jak–Stat3 signalling axis as a potential therapeutic target in lung cancer.[4] To identify the potential driving actors behind metastatic dissemination, the genes enriched in metastases were compared with those obtained from non-metastatic primary tumours. The authors selected 23 of the most differentially expressed genes between metastatic and non-metastatic tumours for which prometastatic activity had not been described previously, and modulated their activity in a functional in vivo model. Interestingly, the knockdown of CD109, a glycoprotein expressed in the surface of T cells and activated platelets, as well as progenitor haematopoietic cells, was able to significantly reduce lung and liver metastases by more than 90% in those in vivo models. They also found that cells lacking CD109 have decreased clonal growth and migration when compared with wild-type cells, which suggests that CD109 plays a role in the initiation of the metastatic cascade. Gene expression profiling showed that CD109 knockdown blocks STAT3 signalling and JAk1 proved to be the main regulator of STAT3. A more detailed study of the CD109–JAk1–STAT3 axis could open a new way for the development of new targeted therapies, tackling the mechanisms that make metastatic disease to occur.

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