which targets the VEGF receptor, as well as MET and AXL tyrosine kinase receptors, which might lead to resistance to antiangiogenic drugs. This choice was probably made because data from a large prospective randomised clinical trial of metastatic renal cell carcinoma progressing after tyrosine kinase inhibitor treatment indicated that cabozantinib outperformed the mTOR inhibitor everolimus in this second-line setting with median progression-free survival of 7·4 months (95% CI 5·6–9·1) versus 3·8 months (3·7–5·4).[8] In the study by Chanzá and colleagues, of the 112 heterogeneous non-clear-cell renal cell carcinoma patients, 26 (23%) did not have surgical resection of the primary tumour, all but nine (8%) had intermediate-risk or poor-risk disease, and 87 (78%) had either previous tyrosine kinase inhibitor or immunotherapy exposure. The proportion of patients who achieved an objective response was 30 (27%) of 112 (*MET*-driven papillary renal cell carcinoma and altered p53 in chromophobe renal cell carcinoma subtypes had higher proportions of responses), one patient with papillary renal cell carcinoma achieved a complete response, median time to treatment failure was 6·7 months (95% CI 5·5–8·6), and the median overall survival was 12·0 months (9·2–17·0). 51 (46%) patients required a dose reduction, but only five (7%) patients discontinued therapy because of toxicity.

Despite the shortcomings of a retrospective cohort study, absence of central pathology and radiology review, and the complex mixture of non-clear-cell tumour histology, this study provides clinicians with credible information that can guide treatment of these notoriously difficult tumours. Because of the rarity of these tumours, large-scale prospective trials that are successful in metastatic clear-cell renal cell carcinoma will be difficult, if not impossible, to do. Yet, the determination of a such a large group of oncologists to provide real-world care to their patients while obtaining and analysing these data is truly remarkable. Extending their work and organisational skills to more centres, awaiting the arrival of more effective systemic agents, and fine-tuning drug selection based on genomics and other biomarkers might allow these investigators the opportunity for future and increasingly effective attempts to tackle these particularly lethal forms of kidney cancer.

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Predicting recurrence in patients with localised renal cell carcinoma after nephrectomy

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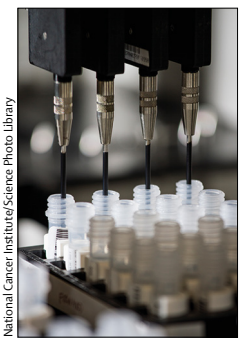
Although most patients who undergo nephrectomy for clear cell renal cell carcinoma for cT1–T3 N0 disease achieve a complete response, up to 30% will recur.[1] Targeted agents and immune checkpoint inhibitors exist that are clinically beneficial for the treatment of metastatic disease and thus there is a motivation to ascertain whether these also provide a benefit in the adjuvant setting.[2] However, successful use of adjuvant therapy depends on several premises. The first is that the benefits of treating those who need therapy (ie, patients with micrometastatic disease) outweigh the risks of treating those whose disease was organ confined and in whom nephrectomy alone had already been successful. The second consideration is that a survival benefit with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adjuvant therapy is only possible if early therapy results in improved survival compared with delayed treatment when the patient already manifests metastatic disease. Although these two steps are crucial for adjuvant therapies to be accepted, identification of patients who should have adjuvant therapy is also an important component to spare unnecessary toxicity in patients who are already likely to be cured by surgery alone.

Several agents have been studied as possible adjuvant treatments for clear cell renal cell carcinoma.[3] Two large adjuvant studies are assessing the efficacy of vascular endothelial growth factor receptor tyrosine kinase inhibitors, with conflicting results. The adjuvant sunitinib trial for patients with high-risk renal cell carcinoma after nephrectomy (S-TRAC) recently published updated results and reported improved disease-free survival for adjuvant sunitinib over placebo across several subgroups, but median overall survival was not reached in either treatment group and no significant differences were observed for that endpoint.[4] The ASSURE trial compared 1 year of adjuvant sunitinib, sorafenib, or placebo in patients with high-grade pathological stage T1b or higher clear cell renal cell carcinoma and found no significant differences in disease-free survival across the treatment groups.[5] A more recent updated analysis of the ASSURE trial in patients with high-risk (pT3, pT4, node-positive) renal cell carcinoma and found no difference in disease-free survival or overall survival between tyrosine kinase inhibitors and placebo, regardless of the prognostic category of the tumour or dose intensity of therapy.[6] The PROTECT trial, which compared placebo with pazopanib, and the ATLAS trial, which compared placebo with axitinib, also did not find an improvement in disease-free survival with these agents. Although these trials have raised questions about the benefits of tyrosine kinase inhibitors, several trials are ongoing or planned to assess the effectiveness of adjuvant immune checkpoint inhibitors for the treatment of renal cell carcinoma, so interest in identifying potential therapies is still strong.[3]

One of the questions raised when comparing the design of the ASSURE and S-TRAC trials involved the selection of patients for adjuvant therapy, since ASSURE recruited patients with pT1 or pT2 disease and S-TRAC enrolled only those with stage 3 or node-positive disease. Ideally, adjuvant therapies would be restricted to patients who have micrometastatic disease and avoided in patients in whom surgery alone had already yielded a successful outcome. Several scoring systems use clinical and pathological data to predict recurrence in patients with renal cell carcinoma, including the University of California Los Angeles integrated staging system, SSIGN, and Leibovich scores.[3] These predictive models have their limitations and so there has been interest in the use of molecular markers to improve prognostication.

In *The Lancet Oncology*, Jun-Huan Wei and colleagues[7] did a validation study to assess the predictive value of single-nucleotide polymorphism (SNP) signatures for recurrence in patients with localised clear cell renal cell carcinoma. The authors analysed a multicentre, retrospective cohort of patients with localised clear cell renal cell carcinoma and developed a six-SNP-based classifier. The area under the curve (AUC) at 5 years of the classifier in the training set was 0·749 (95% CI 0·660–0·826). Notably, the authors assessed SNP signatures in three different regions of the tumour in the training set to account for intratumour heterogeneity. They found different scores in 48 (23%) of 206 cases, but the SNP signature still had similar predictive accuracy for the different regions. The authors then tested the classifier in 217 cases of the internal testing set, in 410 cases of the independent validation set, and in 441 cases of The Cancer Genome Atlas (TCGA) set and found similar predictive accuracy in each of these cohorts. After adjusting for clinical variables (age, sex, TNM stage, Fuhrman grade, and tumour necrosis status) by use of multivariate Cox regression analysis, the six-SNP-based classifier remained a significant, independent prognostic factor for predicting recurrence-free survival and overall survival. Some patients with stage I or II disease with a high-risk classifier were at higher risk of recurrence than those with classifier-defined low-risk pathological stage III disease.

Although this classifier is promising, other published classifiers have independent prognostication in relation to clinical factors. ClearCode34, a 34-gene expression panel, differentiates clear cell renal cell carcinoma into good-risk and poor-risk subtypes with significant differences in recurrence-free survival ($p<0·01$), cancer-specific survival ($p<0·01$), and overall survival ($p<0·01$).[8] Similarly, Rini and colleagues[9] developed and externally validated a 16-gene panel in patients

with stage I–III clear cell renal cell carcinoma who had undergone a nephrectomy. The panel was significantly associated with recurrence after stratifying by stage and adjusting for grade, tumour size, and Leibovich score.

Several obstacles exist to the incorporation of biomarkers into clinical use. First, the benefit of adjuvant therapies needs to be established. Markers that are prognostic might not be predictive such that identifying patients at increased risk of recurrence does not immediately translate into a greater likelihood of them benefiting from therapy. Clinical trials are needed to show a benefit of adjuvant therapies on the basis of markers rather than clinical data alone, which is a difficult challenge. Additionally, there will be regulatory and financial burdens. Despite these obstacles, incorporation of molecular markers into clinical practice is important to facilitate a personalised medicine approach so that patients are not treated with a one-size-fits-all approach, which results in over-treatment for some and under-treatment for others.

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Use of medical cannabis: perceptions of Israeli oncologists

The use of the cannabis plant (*Cannabis sativa*) for the treatment of various cancer-related symptoms, including pain, cachexia, anxiety, and chemotherapy-induced nausea and vomiting, is constantly increasing worldwide.[1,2] The plant contains hundreds of active compounds, of which Δ–9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are considered the most clinically relevant.[2] The activity of the natural plant against cancer-related symptoms has not yet been tested in prospective clinical trials.

Since 2010, Israeli patients with cancer can receive a permit for cannabis use for palliation after a recommendation by their treating oncologist. According to the Israeli Ministry of Health, more than 10 000 patients with cancer receive permits annually, making it the most commonly prescribed medication by the Israeli oncologists. Thus, Israeli oncologists are unique in terms of their vast expertise in the use of cannabis for cancer-associated symptoms.[3,4]

To examine the experience, perceptions, and attitudes of Israeli oncologists towards the use of cannabis, we did a national web-based survey among all those oncologists who are registered with the Israeli Society of Clinical Oncology and Radiation Therapy.

126 (53%) of 238 registered oncologists responded to the survey. Cannabis is extensively used, with 110 (87%) of 126 oncologists prescribing cannabis regularly (table). The indications judged most suitable for starting cannabis were loss of appetite (100 [79%] of 126), nausea (97 [77%]), pain (95 [75%]), and mood disorder (78 [62%]; figure). 115 (91%) of 126 responders have found cannabis effective at least to some degree and most perceived it as safe, with 53 (42%) responders stating they have encountered mild or no side-effects in patients and 63 (50%) responders reporting serious adverse effects but only in a few patients. Despite the extensive use, nearly 90% (111/126) of responders admitted a paucity of