In these and other previous studies of adjuvant therapy within the PORTEC-3 eligibility groups, locoregional failure has been a notable and often predominant failure pattern in the absence of pelvic radiotherapy.

The apparent complementarity of chemotherapy (in limiting distant failure) and radiotherapy (in limiting local failure), is a consistent finding that is a reasonable basis for subsequent clinical investigation. Several studies support the use of combined modality therapy rather than monotherapy.[4,5]

Finally, is there a preferred way of combining chemotherapy with radiotherapy? In both PORTEC-3 and NRG/GOG 258, the combined chemotherapy plus radiotherapy schedule was based on a phase 2 regimen piloted by the Radiation Therapy Oncology Group, RTOG 9708.[6] When NRG/GOG 258 was designed, there was vigorous debate about the combined modality group, with various investigators favoring a sandwich regimen typically involving three cycles of chemotherapy, followed by involved-field radiotherapy, and then additional chemotherapy. The combined therapy approach taken in RTOG 9708 was ultimately chosen, because the data were prospectively obtained. However, multiple studies (retrospective and prospective) have demonstrated the safety and efficacy of the so-called sandwich approach.[5,7–9] Increasing evidence supports the use of upfront systemic therapy, when combined with radiotherapy, as a strategy to maximise both systemic and local control.[10] Many clinicians often use this regimen as a preferred adjuvant approach in locally advanced endometrial cancer.

Based on outstanding work done by the PORTEC Study Group and others, we have made good progress in improving outcomes for women with high-risk and locally advanced endometrial cancers. However, we are not there yet.

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I have received an honorarium from Isoray Medical within the past 2 years.

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The emerging role of PET-CT scan after radical prostatectomy: still a long way to go

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The management of biochemical recurrence after radical prostatectomy is a common challenge for urologists and radiation oncologists, because about 30% of patients have an increase in prostate-specific antigen (PSA) concentrations after surgical treatment.[1] However, the outcome of these patients is not always poor, varying substantially according to the site and the extent of recurrence.[2] In this context, the role of imaging is of the utmost importance to establish the real burden of recurrent disease. The increasing use of PET-CT has led to a shift towards early detection of low-volume metastatic prostate cancer,[3] whereas several novel and promising PET tracers have been reported.[4] However, no prospective clinical trials had tested the superiority of one tracer over the others in terms of diagnostic accuracy.

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In *The Lancet Oncology*, Jeremie Calais and colleagues[5] present a prospective, single-arm, comparative imaging study comparing ^{18}F-fluciclovine PET-CT with ^{68}Ga-prostate-specific membrane antigen (PSMA) PET-CT. The authors should be commended for reporting relevant data in this intriguing field. However, several findings of this study deserve discussion.

The first and most relevant clinical issue is related to the primary endpoint used. Indeed, ^{68}Ga-PSMA showed a significantly higher diagnostic accuracy than ^{18}F-fluciclovine in the field of biochemical recurrence after radical prostatectomy. However, the effect of these findings on subsequent treatment decisions and the related oncological outcomes remains unknown. Nowadays, evidence is emerging to support the role of metastasis-directed therapy in the field of prostate cancer.[6] For example, androgen deprivation therapy (ADT)-free survival was significantly longer in patients treated with metastasis-directed therapy than in those who had surveillance alone in the STOMP trial.[7] Furthermore, the same topic was addressed in the recent SABR-COMET trial,[8] where patients with oligometastatic cancer were randomly assigned to receive either palliative standard of care treatments alone (control group) or standard of care plus stereotactic ablative radiotherapy (SABR group).[8] Despite the fact that only 16 (16%) of 99 patients had prostate cancer, stereotactic ablative radiotherapy was associated with improved overall survival at 1-year follow-up. In this context, the use of PET-CT scan might lead to earlier detection of oligometastatic prostate cancer and improved oncological outcomes. However, future comparative trials addressing therapeutic rather than diagnostic outcomes are needed to assess the real clinical effect of novel PET-CT tracers.

The second clinical issue is related to the observed diagnostic accuracy of the two tracers. In the study by Calais and colleagues,[5] which enrolled 50 patients affected by biochemical recurrence after radical prostatectomy, detection rate was 13 (26%) of 50 patients with ^{18}F-fluciclovine and 28 (56%) of 50 with PSMA. Moreover, ^{68}Ga-PSMA was superior to ^{18}F-fluciclovine at region-based analysis for both pelvic lymph nodes and extrapelvic lesions. However, data from a study of salvage lymph node dissection, with available histological analysis, showed that PSMA substantially underestimates the tumour burden, even at low PSA concentrations.[9] Therefore, despite its higher detection rate, the use of PSMA might translate its underestimation into an undertreatment of the recurrent prostate cancer, especially when metastasis-directed therapies are considered. Taken together, these findings suggest that PSMA has improved the diagnostic accuracy of PET-CT scans, especially at low PSA concentrations. However, it did not solve all the limitations of PET-CT, being less accurate at a relatively low detection rate with a notable underestimation of disease burden.

The third crucial point is the PSA concentration at the time of PET-CT scan. In the study by Calais and colleagues, PSMA was compared to ^{18}F-fluciclovine in participants with PSA concentrations between 0·2 ng/mL and 2·0 ng/mL. This range raises a dual problem. An ideal tracer should perform well at a PSA concentration as low as possible. Indeed, evidence shows that early salvage treatments are associated with better outcomes when delivered at very low PSA concentrations, especially in case of advanced and aggressive disease.[10] As such, a PET-CT scan done at a PSA concentration of more than 0·5 ng/mL—which was the case in about 50% of the patients in the study—might lead to delayed salvage treatments with possible implications on oncological outcomes. By contrast, the PSA concentration of 2·0 ng/mL is an arbitrary cutoff that might exclude a large proportion of patients commonly seen in the daily clinical practice, especially those with highly aggressive disease or extensive nodal involvement. As such, the performance of a specific tracer should be tested and reported at a range of PSA concentrations, without any arbitrary cutoff.

In conclusion, the available PET-CT tracers still have several limitations in the field of recurrent prostate cancer. The introduction of ^{68}Ga-PSMA has improved the diagnostic accuracy of the PET-CT scan, but several issues still persist. Novel tracers and future clinical trials are needed to improve performance.

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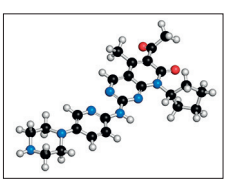
Palbociclib: a new partner for cetuximab?

Recurrent and metastatic head and neck squamous cell carcinoma (HNSCC) remains a substantial health problem. The EGFR-inhibitory monoclonal antibody cetuximab is regularly used in recurrent and metastatic HNSCC, either as monotherapy or in combination with chemotherapy, as part of the EXTREME (platinum-containing agent, fluorouracil, and cetuximab) or TPEx (cisplatin, docetaxel, and cetuximab) regimens, resulting in approximately 13%, 36%, and 46%, of patients achieving objective responses, respectively.[1–3] Unfortunately, these responses are of short duration and median overall survival times have ranged from 10 to 14 months.[1–4] The discovery of adjunctive EGFR-sensitising therapies has therefore become one of the major goals in head and neck oncology research.

In *The Lancet Oncology*, Douglas Adkins and colleagues[5] report the combined results of two of three groups of a non-randomised, phase 2 study evaluating the cyclin-dependent kinases 4 and 6 (CDK4/6) inhibitor palbociclib with cetuximab in recurrent and metastatic HNSCC. This combination was supported by HNSCC gene expression array analysis implicating the retinoblastoma gene (*Rb*) pathway as a compensatory mechanism to EGFR inhibition and by subsequent studies in p16-negative HNSCC cell cultures showing synergy between palbociclib and the EGFR inhibitors afatinib and lapatinib. Adkins and colleagues assessed cetuximab and palbociclib in two groups of patients with recurrent and metastatic HNSCC: cetuximab-naive, platinum-refractory patients (group 1) and cetuximab-resistant patients in whom palbociclib was an attempt to rescue cetuximab sensitivity (group 2).[5] Although the proportions of patients achieving an objective response in the two groups were encouraging (group 1: 39% [95% CI 22–59], group 2: 19% [6–38]) and higher than proportions historically seen for cetuximab monotherapy, duration of response remained short (group 1: 4·0 months [IQR 1·8–5·6], group 2: 6·0 months [2·0–15·5]).[1,5]

Although this uncontrolled study provides a possible signal, limitations remain. Cohort sizes were small, and relevant biomarkers are still scarce. Furthermore, a randomised, placebo-controlled study (PALATINUS), presented in 2019, evaluating the cetuximab and palbociclib combination against single-agent cetuximab in the recurrent and metastatic setting did not produce statistically significant gains in either progression-free survival or overall survival.[6] Two mechanistic points about the combination should also be raised. First, although afatinib and lapatinib both inhibit EGFR, they are not purely EGFR inhibitors and do have off-target effects. These off-target effects can lead to overestimation of the effect size of EGFR-targeted therapy in preclinical systems, falsely attribute the synergy with CDK4/6 inhibitors to an EGFR-specific mechanism, and help to explain discrepancies between expectation derived from the laboratory and clinical reality. Second, in CDK4/6-dysregulated HNSCC patient-derived xenograft models, the CDK4/6 inhibitor abemaciclib shows single-agent activity.[7]

The treatment of recurrent and metastatic HNSCC has not been without progress, and immunotherapy has begun to make inroads.[4,8,9] Most recently, in 2019, KEYNOTE-048[4] compared pembrolizumab monotherapy and pembrolizumab plus chemotherapy with the EXTREME regimen in the first-line setting. Within the subpopulation of patients with recurrent and metastatic HNSCC with a PD-L1 combined positive score of more than 20%, pembrolizumab monotherapy conferred a



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