and progression-free survival was observed for patients younger than 60 years.[6]

The prognostic effect of the cell-of-origin classification also remains uncertain and has been questioned in two prospective trials.[5] Data from the CAVALLI phase 2 trial[7] showed a benefit in adding the BH3 (BCL2 homology 3) mimetic venetoclax to R-CHOP in patients positive for BCL2, irrespective of whether they had the germinal centre or non-germinal centre B cell subtype of disease, suggesting that a single biomarker (BCL2 expression quantified by immunohistochemistry) might be more relevant than cell-of-origin molecular determination for patient selection.[7]

New classifications that integrate next-generation sequencing, fluorescence in-situ hybridisation, or copy number variation data are now available and might offer other therapeutic or predictive opportunities.[8–10] However, these models are complex, partially overlapping, and relatively difficult to test in a randomised clinical trial or apply in daily practice. The selection of diffuse large B-cell lymphoma patients on the basis of biological markers before the first treatment therefore remains a crucial challenge.

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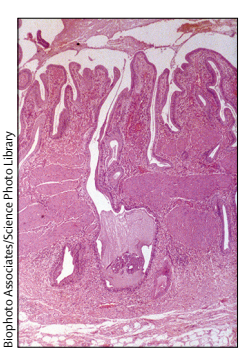
Adjuvant capecitabine in biliary tract cancer: a standard option?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In *The Lancet Oncology*, John Primrose and colleagues[1] have tackled the question of adjuvant treatment for a rare cancer: biliary tract cancer, an unresolved question to date. Although a meta-analysis (of mostly retrospective data) has suggested improved overall survival with adjuvant treatment (especially chemotherapy in patients with node-positive disease and adjuvant radiation-based therapy after R1 resection),[2] older randomised studies were not sufficiently statistically powered to define a standard of care,[3,4] and two recent randomised studies did not show a significant benefit of gemcitabine[5] or gemcitabine plus oxaliplatin (GEMOX regimen).[6]

In the randomised, phase 3, BILCAP study, 753 patients were screened across 44 UK centres between 2006 and 2014, of whom 447 patients with curatively resected cholangiocarcinoma or muscle-invasive gallbladder cancer and preserved performance status (Eastern Cooperative Oncology Group 0 or 1) were randomly assigned to receive oral capecitabine for 24 weeks or observation.[1] Unfortunately, the study did not meet its primary endpoint: the median overall survival by intention-to-treat was 51·1 months (95% CI 34·6–59·1) in the capecitabine group compared with 36·4 months (29·7–44·5) in the observation group (hazard ratio [HR] 0·81, 95% CI 0·63–1·04; p=0·097).

Should capecitabine be considered as ineffective as gemcitabine[5] and GEMOX[6] in the other two recent adjuvant trials? Probably not. In fact, despite being

the largest adjuvant trial in biliary tract cancer so far, the BILCAP study is underpowered, because 2-year overall survival in the observation group (60%) was considerably higher than originally thought (20%). The investigators tried to circumvent this issue by amending their study protocol several times and by modifying their statistical analysis plan. The overall survival benefit became significant in a sensitivity analysis adjusting for sex, disease grade, and nodal status (HR 0·71, 95% CI 0·55–0·92; p=0·010), and in a per-protocol analysis that excluded 17 patients who were either found to be ineligible or were randomly assigned to but did not receive capecitabine (HR 0·75, 95% CI 0·58–0·97; p=0·028). Moreover, intention-to-treat recurrence-free survival was longer with capecitabine (median 24·4 months [95% CI 18·6–35·9] *vs* 17·5 months [12·0–23·8] for observation). However, the risk of relapse differed between treatment groups in the first 24 months (HR 0·75, 95% CI 0·58–0·98; p=0·033), but not thereafter (HR 1·48, 95% CI 0·80–2·77; p=0·21), raising the possibility that capecitabine only defers recurrence. This finding should be further explored when fully mature data are available.

What can be the next steps forward? Ongoing trials will add knowledge about the adjuvant treatment of biliary tract cancer. Given the negative results of the two gemcitabine-based adjuvant trials,[5,6] one might consider testing other fluoropyrimidine-based chemotherapy regimens. S-1, tested in the Japanese ASCOT trial in patients with resected biliary tract cancer, might strengthen the evidence for adjuvant fluoropyrimidines.[7] The multinational ACTICCA-01 trial[8] is testing cisplatin plus gemcitabine (CISGEM regimen), the current standard of care in patients with advanced disease, in patients with curatively resectable disease.[9] Moreover, it also plans to test adjuvant radiotherapy after R1 resection (and no disease progression after adjuvant chemotherapy), with the place of radiotherapy in this setting remaining unclear given the scarcity of randomised data. Neoadjuvant therapy allows treating more patients than adjuvant therapy—only 122 (55%) of 223 patients who received capecitabine in BILCAP completed the planned eight cycles of treatment—however, treatment administration might be hampered by jaundice or the often-complex preoperative management of patients with biliary tract cancer. A molecularly selected trial might also be promising, given the high frequency of targetable alterations in biliary tract cancers; however, the metastatic setting might be a better context to prove this concept.[10]

The British group should be commended for the completion of this statistically negative but clinically meaningful study. The observed overall survival effect size is large (more than 9% at 2 years), and capecitabine is convenient (oral route), affordable (incremental cost per quality adjusted life-year £2725 [US$3538]), and tolerable, with only one patient (<1%) experiencing grade 4 toxicity (cardiac ischaemia or infarction), no treatment-related deaths, and marginal alteration of quality of life. Additionally, recurrent, capecitabine-resistant disease will potentially retain sensitivity to gemcitabine-platinum chemotherapy.[9] Given the negative results of other studies,[5,6] adjuvant capecitabine should be proposed to patients after curative-intent resection of biliary tract cancer, and should be considered the control group for future studies. In that respect, the ACTICCA-1 trial has recently been amended after the results of the BILCAP trial to change the surveillance group for a capecitabine group. However, given the methodological and statistical limitations discussed above, capecitabine cannot be considered an indisputable standard, but rather a standard option. Future efforts to speed up the improvement of outcomes in biliary tract cancer will only be possible through international collaborations.

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DM has received honoraria for lectures from Amgen, Bayer, HalioDx, Merck Serono, Merck Sharpe & Dohme (MSD), Roche, Sanofi, and Servier; honoraria for participation in advisory boards from Agios, Bayer, HalioDx, MSD, Roche, Servier, Shire, and Halio Dx; and travel support from Amgen, Bayer, Merck Serono, MSD, Roche, Sanofi, and Servier. JE reports grants from BTG, and personal fees from AstraZeneca, Bayer, Bristol-Myers Squibb, BTG, Ipsen, and Novartis. He is the coordinating investigator of PRODIGE 12, an adjuvant chemotherapy study in biliary tract cancer, discussed in this comment and the related article.

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Should we expand the carbon ion footprint of prostate cancer?

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Ionising radiation is a known carcinogen, and radiation-related second malignant neoplasia is a complication of radiotherapy with a latency period potentially extending to decades after treatment.[1] Radiation-related second malignant neoplasia might be associated with a worse prognosis compared with sporadic malignancies because of a more aggressive biology of these tumours and the risks imposed by the cumulative toxicities of previous and subsequent treatments.[2,3]

As evidenced by a recent meta-analysis of 21 studies,[4] radiation-related second malignant neoplasia is an uncommon complication in patients with localised prostate cancer after photon radiotherapy; however, the widespread use of this modality in combination with improved overall survival in this setting, early diagnosis, and younger age at treatment will probably increase the prevalence of radiation-related second malignant neoplasia in this population. Understanding the magnitude of the risk and possible ways to mitigate it is, therefore, crucial to an informed discussion with a patient considering radiotherapy or other options for potentially curable prostate cancer.

Unfortunately, reliable data about the relative and absolute risk of radiation-related second malignant neoplasia following radiotherapy in patients with prostate cancer are difficult to obtain. The challenges and pitfalls faced in data collection and interpretation from retrospective databases were previously well described by Wang and colleagues.[5] In addition to large patient cohorts and adequate follow-up (ideally at least 10–20 years) required to identify uncommon events occurring after an appropriate latency period, they recommended that competing risks, including all-cause mortality and non-treatment-related malignancies, be accounted for. With this approach, they identified an increased 10-year incidence of 1% for solid tumours and 0·5% for haematopoietic malignancies following external beam radiotherapy (EBRT) or brachytherapy compared with surgery in patients with prostate cancer. The adjusted hazard ratios for subsequent solid tumour after EBRT (1·931; p<0·001) and brachytherapy (2·072; p<0·001) were significantly increased compared with surgery. Similarly, the adjusted hazard ratios for subsequent haematopoietic malignancies after EBRT (1·504; p<0·001) and brachytherapy (1·214; p=0·012) were also significantly increased compared with surgery. Notably, Krasnow and colleagues[6] reported that the risk of radiation-related second malignant neoplasia in patients with prostate cancer after radiotherapy is largely borne by patients who received treatment at a young age. The incidence ratio of subsequent tumours in those patients who received radiotherapy compared with those who did not was 1·98 [95% CI 1·63–2·41] for patients younger than 55 years, 1·71 [1·60–1·84] for those aged 55–64 years, 1·55 [1·47–1·63] for those aged 65–74 years, and 1·26 [1·09–1·46] for those aged 75 years or older.

Carbon ion radiotherapy was first implemented in Japan 25 years ago and, although its clinical use otherwise remains limited to a few centres in Germany, Italy, and China, additional facilities are under construction worldwide. Treatment volumes with carbon ions are highly conformed to the intended target and allow very little scattered radiation into adjacent normal tissue. The radiation dose distribution of carbon ion radiotherapy is similar to that of proton beam therapy, although carbon ions have a higher relative biological effect than protons or photons.

Mohamad et and colleagues[7] provide data, published in *The Lancet Oncology*, supporting the hypothesis that improved surrounding normal tissue protection during prostate cancer treatment with carbon ion radiotherapy