This idea has similarly been suggested by findings from trials of other EGFR inhibitors.[8,9]

Are these data sufficient to address whether afatinib is better than first-generation EGFR inhibitors? Only head-to-head trials can definitively answer this question and LUX-Lung 7 (NCT01466660), a phase 2b randomised trial comparing afatinib with gefitinib for first-line treatment of lung adenocarcinoma with *EGFR* common mutations, should provide the first comparative evidence of efficacy and safety in this setting. In the absence of direct comparisons, for each patient the choice among the available EGFR inhibitors should take into account all the clinically relevant endpoints, including disease control, survival prolongation, tolerability, and quality of life.

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AR reports personal fees from AstraZeneca and Boehringer Ingelheim. MDM reports personal fees from AstraZeneca and Boehringer Ingelheim.

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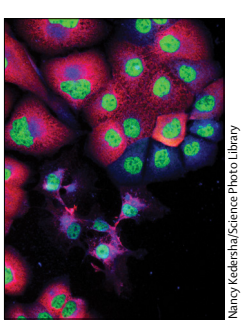
Abiraterone's efficacy confirmed; time to aim higher

In *The Lancet Oncology*, Charles Ryan and colleagues report the final analysis of overall survival from COU-AA-302, a randomised phase 3 trial of abiraterone and prednisone versus placebo plus prednisone in chemotherapy-naive patients with metastatic, castration-resistant prostate cancer.[1] Although improvements in radiographic progression-free survival were previously reported from this trial and those data were sufficient for regulatory approval by several agencies, this confirmation of improved survival reaffirms the importance of secondary androgen biosynthesis inhibition (via CYP17 with abiraterone) in metastatic castration-resistant prostate cancer.[2] The study investigators randomly assigned 1088 minimally symptomatic, chemotherapy-naive patients to receive abiraterone with prednisone or placebo with prednisone. After a median follow-up of 49·2 months (IQR 47·0–51·8) and 741 reported deaths, patients receiving abiraterone had improved overall survival compared with those who received placebo (34·7 months [95% CI 32·7–36·8] for abiraterone *vs* 30·3 [28·7–33·3] months for no abiraterone; HR 0·81, 95% CI 0·70–0·93, p=0·0033).[1] These data are even more remarkable given that 238 (44%) of the 542 patients randomly assigned to placebo plus prednisone were ultimately treated with abiraterone, suggesting that this reported survival advantage is an underestimate. Also noteworthy is that abiraterone significantly delayed the need for opiates (33·4 months [95% CI 30·2–39·8] *vs* 23·4 months [20·3–27·5]; HR 0·72, 95% CI 0·61–0·85, p<0·0001). The toxicity report with extended follow-up remains fairly mild compared with that of chemotherapy, driven mainly by mineralocorticoid (or related) events.

In the past 5 years, seven phase 3 trials—including this study—with five different therapeutic modalities (including anti-androgens, chemotherapy, immunotherapy, and radiopharmaceuticals) have been shown to significantly extend survival in patients with metastatic castration-resistant prostate cancer. This is a remarkable series of advancements that have substantially altered how metastatic castration-resistant prostate cancer is treated.[3] Another therapy, enzalutamide, is an androgen receptor antagonist with greater potency than older androgen receptor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Published **Online** January 16, 2015 http://dx.doi.org/10.1016/ S1470-2045(15)70005-7

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antagonists, and has similarly shown improvements in survival, but, by contrast with abiraterone, does not need prednisone to mitigate mineralocorticoid toxic effects.[4] Along with docetaxel, enzalutamide and abiraterone are the most commonly used treatments for metastatic castration-resistant prostate cancer because of their effects on progression, survival, and tolerability; but, as mentioned by Ryan and colleagues, no data about the ideal sequence or combination of these drugs are available. Some trials investigating this issue are underway, including a phase 3 trial assessing enzalutamide with or without abiraterone in metastatic castration-resistant prostate cancer (NCT01949337).

Emerging data have suggested that abiraterone and enzalutamide, both anti-androgens, have similar mechanisms of resistance. Alternative splicing of androgen receptor transcripts might lead to constituently active androgen receptors that do not require ligands, and is probably a common mechanism of resistance.[5] Over time, clonal selection of these malignant cells with androgen receptor variants could circumvent the therapeutic targeting of abiraterone and enzalutamide. Clinical data now suggest that when enzalutamide and abiraterone are used sequentially, irrespective of order, the second agent has diminished efficacy.[6] Improved understanding of these resistance mechanisms is needed to enable the use of additional therapies sequentially, concomitantly, or for treatment selection. Several clinical trials combining these drugs with chemotherapy, radiopharmaceuticals, and immunotherapy have been initiated in metastatic castration-resistant prostate cancer.

Building on these remarkable advances, future studies will look for ways to deploy these therapies earlier to maximise clinical benefit. The stalwart of metastatic castration-resistant prostate cancer treatment for more than a decade, docetaxel, was shown in 2014 to achieve an impressive improvement in overall survival (17 months) when used with androgen deprivation therapy in high-volume castration-sensitive metastatic prostate cancer.[7] Although this population represents a small proportion of patients with metastatic disease (most patients are castration-resistant at first metastasis), the results emphasise the potential benefits of using effective therapies earlier in the disease course. A similar trial assessing enzalutamide in this population is underway (NCT02058706).

Although noteworthy delays of disease progression are valuable, an increase in the proportion of patients achieving cure is the ultimate goal. Can abiraterone, enzalutamide, or any other emergent therapy enhance the curative intent of radiation or surgery? Can the development of mechanisms of resistance be minimised when tumour volume and heterogeneity are probably low at diagnosis? Preliminary data suggest that these new treatments might have an effect on localised disease. One study combined abiraterone with androgen deprivation therapy in high-risk patients before radical prostatectomy. Patients receiving up to 24 weeks of neoadjuvant androgen deprivation therapy with abiraterone had reduced tumour volume, with one report of a complete pathological response.[8] Similar studies with enzalutamide have been done (NCT01547299), with combination studies planned (NCT02159690). Alternatively, findings from a neoadjuvant study with the therapeutic cancer vaccine sipuleucel-t showed increased immune cell infiltration around the tumour suggesting a localised effect, perhaps providing a rationale for combination studies.[9] Fuelled by the remarkable revolution in therapies for metastatic castration-resistant prostate cancer, a new generation of clinical trials should bring these therapeutic advances to bear on the tumour when it is localised, with hopes of downstaging the disease before radiation or surgery. We should no longer settle for shifting Kaplan-Meier curves in metastatic prostate cancer; instead, we should focus on finding ways to shift paradigms by using these therapies to enhance cure rates at diagnosis.

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We declare no competing interests.

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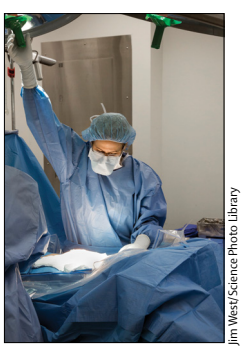
Quality of surgery: has the time come for colon cancer?

Major improvements in outcomes for rectal cancer have occurred in the 30 years since the introduction of total mesorectal excision and multidisciplinary treatment.[1] This situation should continue to improve with more radical surgery for low rectal cancer. Pioneering work by leaders of rectal cancer surgery was initially ignored and it took the independent reproduction of the improved outcomes in single hospital and small regional studies before large-scale regional and national training programmes led to major reductions in local recurrence, significant improvements in survival, and major financial savings occurred around the world.

Colon cancer accounts for around 70% of bowel cancer and although survival has improved, it has not been to the same extent as that for rectal cancer, with substantial variation remaining between hospitals for operative cases. Historical reports have shown significantly improved survival in colon cancer following surgical standardisation,[2–4] and excellent results from Japan have largely been ignored.[5] The rectal cancer story is repeating itself. Colonic cancer resection in western countries is unfortunately still viewed as a routine procedure with little concern surrounding these major variations in outcome. Indeed the focus has been on laparoscopic surgery rather than optimisation of the surgery.

In *The Lancet Oncology*, a paper by Claus Anders Bertelsen and colleagues,[6] and the debate it should generate, is a key step to reproduce the benefits of optimum rectal cancer surgery in colonic cancer, and hints at what could be achievable by the routine adoption of high-quality surgery. In this detailed report, the researchers show that implementation of complete mesocolic excision (CME) with central vascular ligation (CVL) results in a major improvement in survival. By simply visiting and adopting the methods of expert surgeons in Erlangen, led by Werner Hohenberger,[4] and by quality controlling their surgery through mesocolic grading, routine specimen photography, and internal and external pathology audit,[7] the researchers have independently reproduced results from Erlangen and Japan.

The improvement in outcome described could be attributable to two specific variables; first, CME, which comprises the intact removal of the mesocolon and its lymphatic drainage within embryological planes. This procedure should be routine; it does not increase risks to the patient and might seem obvious since careful dissection following anatomical planes is a basic principle of surgery and such planes were described in the early 20th century, but on close scrutiny surgical planes are very variable and must be improved.[8,9] Second, but more controversially, is the role of CVL. This procedure entails more radical central dissection, with potential risk to major vessels, nerves, and organs such as the pancreas. In Erlangen, Japan, and now in Hillerød, such surgery seems to be safe, but several important questions remain. How much benefit does it convey in addition to mesocolic surgery? What is the learning curve and is this achievable for all surgeons? Can it be safely achieved laparoscopically? Is the same benefit derived for all stages of disease? If the emerging evidence from other centres is positive, we need a large, international randomised trial of CME (in all patients), with or without CVL. This type of study would not be possible in Japan where CVL is already mandated in patients with stage III disease and considered in those with stage II disease. Such a trial would inform us of the degree of additional benefit from CVL and the potential complications outside centres of surgical excellence. The trial must have high-quality radiological and pathological studies to identify our accuracy at staging, and the extent and quality of surgery achieved. The role of optimal colonic surgery relative to preoperative treatment with chemotherapy must also be investigated because the combination of preoperative radiotherapy and mesorectal surgery led to additional benefit in MRC CR07.[10]



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Published **Online**
December 31, 2014
http://dx.doi.org/10.1016/S1470-2045(14)71223-9

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