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The importance of local control in pancreatic cancer

Edgar Ben-Josef and Theodore S. Lawrence

The ECOG E4201 study adds another piece of information to a growing body of evidence pointing strongly to the importance of local control and the role of radiotherapy in unresectable pancreatic cancer. Based on this evidence, we believe radiotherapy should be used routinely in this setting.

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The role of radiotherapy in unresectable adenocarcinoma of the pancreas has been in question for the past three decades. Radiotherapy can palliate common symptoms such as pain, duodenal ulceration and bleeding but its impact on survival has not been clear. Whereas older trials were inconclusive, the recent phase III trial reported by Loehrer et al.[1] has shown that radiotherapy improves overall survival when added to gemcitabine. Patients with non-metastatic unresectable adenocarcinoma of the pancreas were randomly assigned to receive gemcitabine alone (1000 mg/m^2 per week for 6 weeks, followed by 1 week rest, then five more cycles of 1000 mg/m^2 for 3 out of 4 weeks) or gemcitabine (600 mg/m^2 per week) concurrently with three-dimensional conformal radiotherapy (50.4 Gy in 28 fractions) followed by additional gemcitabine (five cycles of 1000 mg/m^2 for 3 out of 4 weeks). The study was closed early owing to poor accrual but, in the 74 patients enrolled, median survival improved from 9.2 months to 11.1 months (P=0.017). This came at a cost of increased frequency of grade 4 toxic effects (although combined grade 3 or 4 toxic effects were the same in each arm). These results lend support to the notion that radiation therapy improves the survival of patients with unresectable pancreatic cancer through intensification of local therapy, given that uncontrolled local growth is the cause of death in 30% of patients with this malignancy.[2]

The trial conducted by Loehrer et al.[1] is one of two trials conducted in this decade addressing the question of whether radiotherapy can be of benefit in unresectable adenocarcinoma of the pancreas. The other study, the Fédération Francophone de Cancérologie Digestive and Société Française de Radiothérapie Oncologique (FFCD–SFRO) trial[3] showed a worse survival (8.6 months vs 13 months; P=0.03) when chemoradiotherapy was added to gemcitabine. However, the chemoradiotherapy regimen tested in that trial (60 Gy in 30 fractions in 6 weeks concomitant with a 5-fluorouracil infusion [300 mg/m^2 per day] days 1–5 for

6 weeks and cisplatin [20 mg/m^2 per day] days 1–5 on weeks 1 and 5) was highly toxic (65.5% grade 3 or 4 toxic effects) and, no doubt, contributed to the worse outcome.

Unfortunately, radiotherapy has been used suboptimally in this disease. The sensitivity of the organs to radiotherapy in the upper abdomen has limited the radiation dose to ineffective levels, and attempts to increase the radiation dose have been unsuccessful, resulting in high morbidity and mortality.[4]

An alternative strategy is to use radiosensitising drugs that enhance the effect of radiation preferentially within the tumour. The two drugs that are used most commonly with radiation in the treatment of pancreatic cancer, gemcitabine and 5-FU, both appear to decrease the ability of cancer cells to repair radiation-induced DNA damage.[5] At the University of Michigan we have carried out a series of trials using full therapeutic doses of gemcitabine – a potent radiosensitiser[6] – and concurrent three-dimensional conformal radiotherapy to maximise systemic and local control. However, toxicity has prevented the escalation of the radiation dose beyond 36 Gy in 2.4 Gy fractions even when only the tumour was targeted and clinically negative lymph nodes were excluded.[7]

> **"The question now is not whether radiotherapy is of benefit in this disease but rather how to make it more effective"**

An option that might allow delivering an increased radiation dose to the pancreas without exposing the dose-limiting organs to toxic levels of radiation is intensity-modulated radiotherapy (IMRT).[8] For example, we recently completed a trial in which we used IMRT to simultaneously reduce the dose to the stomach and intestines and increase the dose in the tumour in patients with unresectable pancreatic cancer. We have established that high-dose radiotherapy (55 Gy in 25 fractions) can be delivered safely with concurrent full-dose gemcitabine, with the use of IMRT delivered during breath hold. The rate of severe toxicity (24%) observed when using this chemoradiotherapy dose[9] compares favourably with toxic effects reported with other contemporaneous regimens. In addition, there are encouraging signals of efficacy; the median overall survival and two-year overall survival in this trial[9] (14.8 months and 30%, respectively) are significantly better (hazard ratio = 0.63, log-rank P=0.028) than historical controls (11.2 months and 13%, respectively).[10] These results also compare favourably with other contemporary phase II and phase III trials in this patient population, with either 5-FU-based or gemcitabine-based chemotherapy. High-dose radiotherapy also improved the two-year local control from 38% (historical controls)[10] to 59%.[9] Most importantly, 12 of 50 patients (24%) receiving high-dose radiotherapy were able to undergo resection with good outcomes; 10 patients (83%) had R0 resection and five patients (42%) had a major pathological response. The median survival in these patients who had undergone resection was 32 months.[9]

Thus, the results from the Eastern Cooperative Oncology Group (ECOG) trial[1] coupled with the finding that a significant proportion of patients with pancreatic cancer die of complications of uncontrolled growth,[2] and results showing improved local control and survival in patients receiving high-dose radiotherapy, suggest a new paradigm. The question now is not whether radiotherapy is of benefit in this disease but rather how to make it more effective and how to combine it optimally with systemic therapies.

A number of strategies can be explored to further intensify local therapy. Firstly, improvements in radiotherapy planning and delivery: we need to improve targeting of the tumour while avoiding the critical normal tissues and to incorporate individual susceptibilities to radiation toxicity into treatment planning. Secondly, we have to explore the use of novel tumour-specific radiosensitisers: with so many targeted agents in the pipeline, this strategy is more promising than ever. Potential candidates include CHK1 inhibitors, nab-paclitaxel, PARP inhibitors, MEK inhibitors, and many others. Thirdly, we have to carefully study the potential role of surgery in selected patients.

Finally, potential progress can be made by individualising therapy. One such effort underway is an attempt to use the status of SMAD4 (also known as DPC4) to select patients for intensive local therapy versus intensive systemic therapy. Loss of DPC4 is associated with a widely metastatic phenotype, while patients with intact DPC4 are more likely to die of local complications.[2] Thus, in a currently planned national trial, DPC4 status will be determined upfront by cytology. Patients with

Practice point

Radiation therapy with gemcitabine improves the survival of patients with non-metastatic unresectable pancreatic cancer compared with gemcitabine alone. Therefore, gemcitabine combined with radiation can be considered a standard of care for these patients.

intact DPC4 will be randomly assigned to receive an intensive or a standard chemoradiotherapy regimen (following 12 weeks of gemcitabine) whereas patients with DPC4 loss will be randomly assigned to receive FOLFIRINOX (5-fluorouracil, leucovorin, irinotecan and oxaliplatin) versus gemcitabine (followed by standard chemoradiotherapy) for two weeks.

In summary, the current ECOG trial adds one more piece of information to a growing body of evidence pointing strongly to an important role of radiotherapy in local control for unresectable pancreatic cancer. Future advances could come from better selection of patients for intensive local therapy using molecular biomarkers.

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Time for another rethink on prostate cancer screening

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Screening for prostate cancer using PSA is a careful balance of benefits and harms. But current US practice involves testing older men who have little to gain and aggressively treating low-risk cancers. Debates about whether to test need to be replaced by debates on how to test better.

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The US Preventive Services Task Force (USPSTF) recently issued a recommendation against the use of prostate-specific antigen (PSA) testing for prostate cancer screening.[1] They concluded that "there is moderate or high certainty that [prostate cancer screening] has no net benefit or that the harms outweigh the benefits." In this article, we review the USPSTF report and make three simple points. First, the USPSTF report is riddled with errors, so much so that we would be sympathetic to accusations that the task force was biased. Second, if the USPSTF were indeed biased against PSA screening, this would be entirely understandable: urologists, radiation oncologists and others have made such a mess out of PSA screening that it is easy to see why a group of family practitioners, obstetricians and paediatricians would like to write the whole thing off. Third, PSA screening can be done in different ways, and the ratio of benefit to harm will depend on choices regarding how PSA tests are used. As mid-life levels of PSA are strongly predictive of long-term risk of prostate cancer morbidity,[2,3] we would argue for risk-stratified approaches, to minimise harms for men unlikely to benefit from screening and ensure careful follow up of those at the highest risk of unfavourable outcome.

Regarding our first point, the USPSTF report is riddled with errors of fact, interpretation and statistics. Some of these errors might be considered understandable. Take, for example, the claim that in the interim report from the European randomised screening trial (ERSPC) after a median follow up of 9 years,[4] "48 men received treatment for every prostate cancer-specific death prevented." The number of 48 patients was obtained by dividing the between-group difference in prostate cancer diagnoses with the between-group difference in cancer deaths. As not all men diagnosed with prostate cancer in this study were treated — some were placed on

active surveillance — the USPSTF statement is incorrect. It is also highly misleading, as the ratio of diagnoses to deaths that are avoided is time dependent; consider that this ratio is infinity at early follow up because screening does not prevent death in a man diagnosed with advanced-stage cancer at his first PSA test. The empirical estimate from the Göteborg arm of ERSPC, which has longer follow up (14 years) is that 12 men need to be diagnosed to prevent one death from prostate cancer.[5] Still, the ERSPC report[4] used the phrase "number-needed-to-treat" and cited the number 48, so perhaps the USPSTF error is understandable.

The principal flaw of the USPSTF might also be seen as an understandable mistake. Specifically, the USPSTF draws definitive conclusions of "moderate or high certainty of no benefit" on the basis of interim data: the largest randomised trial of prostate cancer screening – the European ERSPC trial – has not yet reported on the main endpoint of cancer-related mortality at its prespecified primary timepoint, data were only reported because the difference between groups crossed a prespecified significance boundary at interim analysis. It seems bizarre to be certain of "no benefit" when a major trial is yet to report in full.

What is less understandable is that the USPSTF make unsupportable claims that seem designed to emphasise that screening is harmful and that there should be less of it. For example, the USPSTF cites a perioperative mortality rate from radical prostatectomy of 0.5%, far higher than most contemporary estimates, such as 0.1%.[6] This is because they used a study of Medicare patients to draw their conclusions, that is, the oldest patients at highest risk for perioperative death. In addition, it is hard to understand the biological mechanism behind the claim that because "the [negative US] trial evaluated a shorter screening interval [than the positive European trial] ... more conservative screening and treatment strategies might be more effective than more aggressive ones."[1] Less regular screening may well decrease the harms of screening, but there is simply no mechanism by which it could be more effective.

Our second point is that contemporary PSA screening and treatment is a farrago and so if the members of the USPSTF were indeed prejudiced against PSA screening, it is not hard to see why. There is a lot to dislike about how prostate cancer is detected and managed in the US. For example, PSA screening is routinely used in men who have nothing to gain from it, with testing applied to one-third of men aged over 70 years who have a greater than 50% risk of death within five years.[7] In addition, digital rectal examination is widely used even though it is not informative in a screening setting.[8] Urologists are then extremely quick to biopsy, with current guidelines recommending biopsy for almost any indication: a raised PSA, a lowered ratio of free-to-total PSA, a high PSA velocity or a positive digital rectal examination. Worst of all, radiotherapy or surgical treatment is almost universally recommended: empirical studies show that fewer than 10% of men with low-risk disease are offered active surveillance.[9] Couple this with apparent conflicts of interest, such as groups of urologists purchasing radiation equipment and then self-referring patients, and it is not hard to see why those outside of the prostate cancer field see PSA testing as nothing more than a scam.

> **"...current PSA testing as it is commonly practised in the US is indefensible"**

Prostate cancer screening is not a single intervention, such as a certain dose of a specific drug; it can be implemented in numerous different ways. Starting PSA screening at, say, 70 years, using a very low PSA threshold for biopsy and then aggressively treating all cancers will lead to enormous amounts of overdiagnosis and overtreatment and will have little effect on mortality. Conversely, focusing on younger men, only biopsying those meeting stringent criteria, and managing low-risk cancers by active surveillance will lead to a better balance of harms and benefits. Indeed, given the diversity of approaches to PSA screening and subsequent management of PSA-detected tumours, it is hard to know whether it is even coherent to make statements such as "PSA screening is associated with a 42% rate of overdiagnosis" or "48 men need to be diagnosed after a PSA test to save one life".[1]

We would argue that the interim analysis of ERSPC and prespecified analysis from the Göteborg randomised trial in Europe demonstrates that PSA-based screening can reduce cancer-specific mortality and, as such, our question should really be how to make it work better. A key method will clearly be risk stratification: focusing PSA screening on the men at highest risk of prostate cancer morbidity and mortality will improve the ratio of benefit to harms. As it turns out, the most powerful risk factor is PSA itself.[2,3] Indeed, re-analyses of the European ERSPC trial suggest that

Practice points

The outcomes of PSA screening could be dramatically improved by:

- Avoiding screening in older men (age ≥70 years)
- Use of active surveillance to manage low-risk disease

if men with a low baseline PSA level were exempted from further screening, there would be a dramatic reduction in the number of men screened, biopsied, diagnosed and treated per prostate cancer death avoided.[10]

In summary, the question is should we abandon PSA testing? One answer might be that yes, we should: current PSA testing as it is commonly practised in the US is indefensible. However, we should avoid throwing out the baby with the bathwater and instead grasp the opportunity to implement a more-rational, risk-stratified approach to PSA screening, which avoids testing of men with little to benefit and uses active surveillance to manage low-risk prostate cancer. Such a strategy has the best chance to reduce prostate cancer mortality while minimising overdiagnosis and overtreatment.

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Competing interests statement

Hans Lilja is an inventor and owner of patents WO 0227323, US 2002123616, WO 0193861, WO 9201936, WO 9626442, EP 0635575, and DE 9117047. Andrew J Vickers declares no competing interests