Radical prostatectomy versus observation for prostate cancer

In the July 19, 2012, issue of the *New England Journal of Medicine*, investigators from the Prostate Cancer Intervention Versus Observation Trial (PIVOT) group reported results of a study that asked whether radical prostatectomy improved survival in men with prostate cancer when compared with observation.

Results from PIVOT showed that, in men with localised prostate cancer diagnosed between 1994 and 2002 (the early era of prostate-specific antigen [PSA] testing), radical prostatectomy did not significantly reduce all-cause or prostate-cancer mortality compared with observation.

"Absolute differences in mortality between the study groups were less than 3 percentage points", said lead author Timothy Wilt (Minneapolis VA Health Care System and University of Minnesota, Minneapolis, MN, USA).

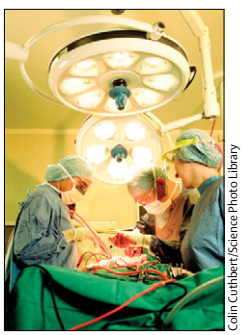
"Compared with observation, radical prostatectomy did not significantly reduce all-cause or prostate-cancer mortality among men with clinically localised tumours through at least 12 years of follow-up", he added. This finding is consistent with other studies of active surveillance in men with low-risk tumours who were given treatment only if they developed high-risk cancer.

"PIVOT provides the best data currently available on the benefit, or lack of benefit, of radical treatment for localised prostate cancer", according to Chris Parker (The Royal Marsden, London, UK)." He continued: "The trial suggests a worthwhile survival benefit for surgery in men with high-risk disease, but little or no benefit to men with low-risk disease. Men with low-risk disease can have a good prognosis, even without treatment."

In an accompanying editorial, Ian M Thompson Jr and Catherine M Tangen questioned the study's power. "With an actual enrolment of 731 patients, the study was underpowered to detect this relatively large clinical effect", they said.

Wilt strongly disagrees. "Our data supports the robustness of our results", he said. "PIVOT is the largest and longest randomised controlled trial ever conducted of treatment for men with primarily PSA-detected prostate cancer. For the vast majority of men with early-stage prostate cancer, choosing observation can help them live a similar length of life, avoid death from prostate cancer, and prevent the harms related to early intervention with surgery." He added: "Physicians can now recommend observation as a preferred treatment choice for most men, especially those with PSA values of 10 or less".

Jim Mullins



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For more on **PIVOT** see *N Engl J Med* 2012; **367:** 203–13

For more on the **accompanying editorial** see *N Engl J Med* 2012; **367:** 270–71

Therapeutic drug targets in colorectal cancer

The Cancer Genome Atlas Network has done a comprehensive analysis of genomic alterations in human colon and rectal adenocarcinomas and has identified several potential therapeutic targets.

16% of colorectal carcinomas from 224 patients were hypermutated, and this subset of tumours had a median of 728 mutations, compared with a median of 58 mutations in the non-hypermutated carcinomas. Very similar patterns of genomic changes were reported across the entire non-hypermutated group of colon and rectal carcinomas—two cancers that are typically thought to be different entities, and thus are treated by different therapeutic approaches.

When asked how the results of this study might change the treatment of colorectal cancer, study author Raju Kucherlapati (Paul C Cabot Professor of Genetics and Professor of Medicine, Harvard Medical School, Boston, MA, USA) replied, "[In] a number of ways. From a clinical point of view, there has been a question as to whether these tumours are clinically distinct. At the molecular level, we cannot distinguish between these two cancers. This has significant ramifications moving forward. There are drugs already approved or in development [that may be effective] for both colon and rectal cancers."

He continued, "This study has shown that there are a number of pathways that are deregulated. For example, 5% of tumours have *ERBB2* amplification, which suggests that these patients may respond to trastuzumab. A completely new finding is that 20% of patients have overexpression of *IGF2*; there are drugs against this in clinical trials. Nearly 100% of tumours have alterations in the WNT signalling pathway; currently there are drugs [targeting this pathway] in development. This cancer currently has little targeted therapy—this study opens up many possibilities."

Commenting on the results of this study, James Willson (director of the Simmons Comprehensive Cancer Center, University of Texas Southwestern Medical Center, Dallas, TX, USA) said, "Having worked in understanding the biology of colorectal cancer, there's been a tremendous amount of progress. What is exciting about this study is that it has expanded this knowledge and given it greater focus."

He added, "We'll need to develop combinations of therapeutics; these data will give us much more information on how to develop these combinations. This is an iterative process."

Judith A Gilbert

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For more on the **colorectal cancer study** see *Nature* 2012; **487:** 330–37