Salvage radiotherapy with or without short-term hormone therapy for rising prostate-specific antigen concentration after radical prostatectomy (GETUG-AFU 16): A randomised, multicentre, open-label phase 3 trial.


Take-Home Message
This is a French, multicentre, open-label, phase 3 controlled trial of 743 men with previously treated adenocarcinoma of the prostate who were randomized to receive standard salvage radiotherapy, intensity-modulated radiotherapy, or radiotherapy plus short-term androgen suppression using 10.8 mg subcutaneous goserelin (administered on the first day of irradiation treatment and 3 months later). The study included patients who had undergone previous radical prostatectomy and had rising PSA levels, but no evidence of clinical disease. Patients were not eligible if they had had previous pelvic radiotherapy or androgen deprivation therapy. Patients who received a combination of goserelin and radiotherapy had reduced risk of biochemical and clinical progression at 5 years compared with those who received radiotherapy alone (p<0.0001). There were no treatment-related deaths. Acute adverse events associated with goserelin included hot flushes, sweating, or a combination. Grade 2 or worse adverse events occurred in 8% of 366 patients treated with goserelin.

This phase 3 trial demonstrated benefits to the use of androgen suppression in combination with radiotherapy for men who have undergone radical prostatectomy and experienced PSA level increases after having undetectable levels during the postsurgical period.

Abstract
Background:
How best to treat rising prostate-specific antigen (PSA) concentration after radical prostatectomy is an urgent clinical question. Salvage radiotherapy delays the need for more aggressive treatment such as long-term androgen suppression, but fewer than half of patients benefit from it. We aimed to establish the effect of adding short-term androgen suppression at the time of salvage radiotherapy on biochemical outcome and overall survival in men with rising PSA following radical prostatectomy.

Method:
This open-label, multicentre, phase 3, randomized controlled trial, was done in 43 French study centres. We enrolled men (aged ≥18 years) who had received previous treatment for a histologically confirmed adenocarcinoma of the prostate (but no previous androgen deprivation therapy or pelvic radiotherapy), and who had stage pT2, pT3, or pT4a (bladder neck
involvement only) in patients who had rising PSA of 0.2 to less than 2.0 μg/L following radical prostatectomy, without evidence of clinical disease. Patients were randomly assigned (1:1) centrally via an interactive web response system to standard salvage radiotherapy (three-dimensional [3D] conformal radiotherapy or intensity modulated radiotherapy, of 66 Gy in 33 fractions 5 days a week for 7 weeks) or radiotherapy plus short-term androgen suppression using 10.8 mg goserelin by subcutaneous injection on the first day of irradiation and 3 months later. Randomization was stratified using a permuted block method according to investigational site, radiotherapy modality, and prognosis. The primary endpoint was progression-free survival, analysed in the intention-to-treat population.

Results:
Between Oct 19, 2006 and March 30, 2010, 743 patients were randomly assigned, 374 to radiotherapy alone and 369 to radiotherapy plus goserelin. Patients assigned to radiotherapy plus goserelin were significantly more likely than patients in the radiotherapy alone group to be free of biochemical progression or clinical progression at 5 years (80% [95% CI 75–84] vs. 62% [57-67]; hazard ratio [HR] 0.50, 95% CI 0.38–0.66; p<0.0001). No additional late adverse events occurred in patients receiving short-term androgen suppression compared with those who received radiotherapy alone. The most frequently occurring acute adverse events related to goserelin were hot flushes, sweating, or both (30 [8%] of 366 patients had a grade 2 or worse event; 30 patients [8%] had hot flushes and five patients [1%] had sweating in the radiotherapy plus goserelin group vs. none of 372 patients in the radiotherapy alone group). Three (8%) of 366 patients had grade 3 or worse hot flushes and one patient had grade 3 or worse sweating in the radiotherapy plus goserelin group versus none of 372 patients in the radiotherapy alone group. The most common late adverse events of grade 3 or worse were genitourinary events (29 [8%] in the radiotherapy alone group vs. 26 [7%] in the radiotherapy plus goserelin group) and sexual disorders (20 [5%] vs. 30 [8%]). No treatment-related deaths occurred.

Conclusion:
Adding short-term androgen suppression to salvage radiotherapy benefits men who have had radical prostatectomy and whose PSA rises after a postsurgical period when it is undetectable. Radiotherapy combined with short-term androgen suppression could be considered as a reasonable option in this population.