

patients treated with RN only, 33 of 365 had palpably enlarged LNs, of which 4 (12%) had metastatic spread.

Expert's comments:

The eagerly awaited results of this randomized study show clearly that in patients without clinically detectable LNs and distant metastases, there was no difference in progression-free or overall survival, whether or not LN dissection was performed. The patients, accrued between 1988 and 1991, were evaluated preoperatively with computed tomography (CT) and chest x-ray. Due to the advances of the imaging techniques, one might suspect that most of the palpably enlarged LNs should have been diagnosed by CT today [1]. The palpably enlarged LNs contained metastases in 14 of 84 patients (17%)—results comparable to 42% metastases in enlarged LNs detected by CT [2]. Only 1% of patients without palpable LNs had metastases after LN dissection. Due to the increased detection of asymptomatic renal tumors, a stage shift is evident, with a majority of those with RCCs ≤ 4 cm having improved survival [3]. Therefore, in the majority of RCCs today, there is no indication for LN dissection.

The question of whether LN dissection should be performed in patients with enlarged and/or metastatic LNs was not answered by the present study. In patients with nonmetastatic RCC having palpable or

CT-detected enlarged LNs, LN dissection should not be abandoned, since adequate staging information is needed [4]. Such information is necessary for risk-group classification and, thus, is important for prediction of survival and for future adjuvant treatment protocols.

Conflicts of interest: The author has nothing to disclose.

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Re: Sequence Variant on 8q24 Confers Susceptibility to Urinary Bladder Cancer

Kiemeny LA, Thorlacius S, Sulem P, et al

Nat Genet 2008;40:1307–12

Expert's summary:

The authors performed an exhaustive study to identify single-nucleotide polymorphisms (SNPs) associated with bladder cancer. They initially genotyped 1803 cases and 34 336 controls for 302 140 SNPs. Ten SNPs were significant at a lower-than-defined threshold ($p < 5 \times 10^{-5}$) and were then genotyped in a new cohort of 2165 cases and 3800 controls. The strongest associations with bladder cancer were found with a SNP at 8q24.21 (rs9642880; odds ratio [OR]: 1.22; $p = 9 \times 10^{-12}$) and one on 3q28 (rs710521; OR: 1.19; $p = 1.15 \times 10^{-7}$). The 8q24 SNP is 30 kb downstream of the *c-Myc* oncogene and close to a predicted gene (known as BC042052). Approximately 20% of European individuals are homozygous for rs9642880[T],

and their risk of developing urinary bladder cancer is 1.49 times that of noncarriers.

Expert's comments:

Genetic epidemiology is undergoing a revolution. Textbooks illustrate inheritance and disease risk using Mendelian principles with uncommon high-risk genes (eg, *BRCA1*). Inherited mutation of these genes usually results in loss of function and cancer. However, for most cancers, it is common and low-risk gene variants (known as SNPs, which alter rather than ablate function) that determine cancer risk (plus environmental factors) [1]. This hypothesis supports observations that most cancers occur outside cancer families, and an individual's risk of cancer increases modestly if a direct relative is affected (eg, OR of 1.24 for bladder cancer [2]). Kiemeny et al studied a large European population for 302 000 SNPs of the 14.7 million currently known. They did not identify a coding SNP (one that changes a gene's sequence) at their statistical threshold but did find several non-

coding SNPs highly associated with the disease. Whilst at first this may appear to be disappointing, many positive findings can be elicited. First, these data suggest that a familial bladder cancer gene does not exist. Second, the modest risk attributed to the SNP suggests that environmental factors are far more important than genetic factors for bladder cancer (changing behaviour could reduce burden). Third, one can identify homozygous individuals at whom to target health promotion. Finally, these findings potentially point to new methods of genetic susceptibility. Studies in breast, colon, and prostate cancer (referenced in Ghossaini et al [3]) have all identified SNPs within the 8q24 region that predispose to their respective cancers. Why these tumours all share this region, in which there are few genes, is unclear. Could this region mark a distant genetic event or represent part of the machinery of an unknown molecular control mechanism?

Conflicts of interest: The author has nothing to disclose.

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Re: The Efficacy and Safety of Degarelix: A 12-Month, Comparative, Randomized, Open-Label, Parallel-Group Phase III Study in Patients with Prostate Cancer

Klotz L, Boccon-Gibod L, Shore ND, et al

BJU Int 2008;102:1531-8

Experts' summary:

This study is the first published phase 3 trial on degarelix, a gonadotropin-releasing hormone (GnRH) antagonist for the treatment of advanced prostate cancer. Between February 2006 and October 2007, a total of 620 patients with prostate cancer of various stages were randomized to receive degarelix 240 mg subcutaneously (SC) followed by 80 mg SC every 4 wk (arm A) or degarelix 240 mg SC followed by 160 mg SC every 4 wk (arm B) or leuprolide 7.5 mg by intramuscular injection (IM) every 4 wk (arm C) for a total study period of 1 yr.

The primary end point (ie, testosterone suppression to a predefined castrate level of ≤ 0.5 ng/ml from day 28 to day 364) of this noninferiority open-label trial was reached in 96-98% of patients without a difference between the study groups. Results for a total of 14 different secondary end points also showed comparable results with a few exceptions. As expected, testosterone and prostate-specific antigen (PSA) in arms A and B declined earlier

compared with arm C. At day 3, the predefined castration level was reached in 96.1% and 95.5% of patients in arms A and B, respectively, while patients in arm C demonstrated a testosterone elevation of 65% from baseline. At days 14 and 28, PSA levels had respectively declined by 64% and 85% in arm A, by 65% and 83% in arm B, and by 18% and 63% in arm C. While most adverse events were comparable among the study groups, 40% of patients receiving degarelix experienced pain at the injection site compared with <1% in the leuprolide group. Additionally, 4% of patients experienced chills following the application of degarelix compared with zero in the leuprolide arm.

Experts' comments:

For a long time, GnRH antagonists demonstrated insufficient water solubility and induction of allergic reactions [1]. Indeed, the first approved GnRH antagonist, abarelix, was associated with systemic allergic reactions in 1-3% of patients. Degarelix does not seem to be associated with this problem.

Degarelix ran through various phase 1 and 2 trials, and dose finding was a major goal of these trials [2]. Now, the ideal dose seems to be known and noninferiority to leuprolide could be demonstrated in the discussed trial. Despite so many end points in this trial, progression-free survival, cancer-specific survival, and overall survival were not addressed.