In this issue of *European Urology*, Popiolek and co-authors [1] present the final analysis of a historic landmark study initiated by Johansson et al. [2]. Between 1977 and 1984, 223 patients were diagnosed with organ-confined prostate cancer (PCa) for which they did not receive immediate treatment. In 106 of these patients, so-called clinically occult PCa was diagnosed by histopathology from transurethral resection or open prostatectomy material obtained after the patients presented with obstructive voiding symptoms. In 72 patients, PCa accounted for <25% of the examined material, in 34 patients it accounted for >25%. In the remaining 117 patients, clinically palpable disease was confirmed by fine-needle aspiration biopsy [2].

After a 10-yr follow-up, Johansson et al. noted that only 8.5% of the 223 patients who had died of PCa; 85% of the 124 total deaths were from other causes. Patients with undifferentiated PCa were most at risk to die. A surprisingly low PCa-specific mortality rate was noted for patients with highly or moderately differentiated tumors [3]. These findings were by and large confirmed when analyzing the 15-yr survival, showing that patients with localized PCa had a favorable outlook following watchful waiting, and the researchers concluded that “the number of deaths potentially avoidable by radical initial treatment is limited” [4].

In 2004, after a mean observation period of 21 yr, Johansson et al. noted that local tumor progression and aggressive metastatic disease may be found after >15 yr in patients initially diagnosed with moderately differentiated cancer and, rarely, in patients diagnosed with grade I cancer. This is basically confirmed in the final analysis by Popiolek et al. after all but three of the 223 men had died. All told, 38 of 223 men (17%) died of PCa. This number includes all nine men with Gleason grade 8–10 disease and also includes some men who died >15 yr after initial diagnosis of apparently well-differentiated tumors.

The authors are to be commended not only for having vigorously conducted the study according to the treatment policies of the 1980s but also for having followed the patients until death. The final results differ somewhat from the initially estimated outcomes. With this, Popiolek et al. reconfirm that a long observation period (15–20 yr) may be necessary for conclusive assessment of treatment outcomes in PCa.

When interpreting the results of this landmark study, several points must be considered. First, the results do not necessarily reflect “the natural history of early, localized prostate cancer” [4]. All patients were regularly followed, making it unlikely that they suffered severe complications from untreated disease. Second, all patients who became symptomatic or showed progressive disease received some form of hormonal manipulation, usually androgen-deprivation therapy, namely, in the early years of the study, with estrogens or orchietomy [4]. Third, the mean age of the 223 patients when entering the study was 72 yr. As already noted by Johansson et al., the overall results may not apply to younger patients with a life expectancy >15 yr [5]. Fourth, whether some patients with tumors considered low risk are indeed at risk for progressive disease or may even die from it after >15 yr remains a somewhat open question.

As acknowledged by the authors, in some patients, an initial misclassification/grading may be possible, if not likely. Grading based on fine-needle aspiration, as was the case in almost 50% of the patients, may have been less reliable than systematic ultrasound-guided core biopsies from the prostate. Only nine (4%) of all patients were classified as having grade III (undifferentiated) disease, making it likely that some grade I/II tumors were initially misclassified. The fact that the incidence of progression and PCa death was similar between patients with palpable and patients with nonpalpable tumors might also point to difficulties with the initial risk classification. Indeed, in a recent study by Ross...

E-mail address: urs.studer@insel.ch.
et al. on over 14,000 radical prostatectomy specimens, there was not a single case of a Gleason score ≤6 tumor with lymph node metastases [6]. Fifth, at the time of patient recruitment, pelvic nodal status could not be assessed by computed tomography, nor was serum prostate-specific antigen (PSA) level determination possible. Finally, the 15- and 20-yr survival probabilities for good- and intermediate-risk patients were based on a very small number of patients, as reflected by the wide confidence interval limits (Fig. 1 and 2 in Popiolek et al. [1]).

Unfortunately, even after a maximum follow-up of some patients for >30 yr, the Johansson et al. study cannot answer the intriguing question of whether moderately or well-differentiated PCa may become a deadly disease after sufficiently long follow-up. The number of such patients is too small and the possibility of initial undergrading, as acknowledged by the authors, remains an unquantifiable factor. Nevertheless, despite the caveats expressed regarding misclassification and that the so-called low-risk patients of the Johansson et al. study are not comparable to low-risk patients detected more recently in the PSA era based on multiple systematic ultrasound-guided transrectal biopsies, three points deserve our attention. First, although the majority of the 223 patients had either palpable disease or >25% of cancer tissue in the resected prostatic tissue, apparently only 17% of them died of PCa. Second, 64% of these men never required any androgen-deprivation therapy for symptomatic or progressive disease during their life span. Third, to keep the risk of progressive disease low in patients with apparently low-risk disease, repeat biopsies rather than serum PSA monitoring should help reduce the risk of initial misclassification [7].

Conflicts of interest: The author has nothing to disclose.

References