Commentary: Active surveillance as an option for men with localized prostate cancer involves observation without curative treatment, with periodic followup including clinical staging digital rectal examination (DRE), PSA testing and prostate biopsy. This approach attempts to prevent the overtreatment of patients with clinically insignificant cancers, while at the same time treating those with progressive disease with curative intent. Most active surveillance cohorts, like that at Sunnybrook Health Sciences Centre in Toronto, restrict entrance into active surveillance with time in a large, active surveillance cohort with long-term followup. This study of 593 patients from Sunnybrook represents one of the largest active surveillance cohorts to date of patients with localized prostate cancer. As well, with a median followup of 6.4 years (max 20.2 years), this cohort is one of the longest trials reported of men undergoing active surveillance for prostate cancer.

In the Sunnybrook cohort, 31.2% of patients were upgraded to a higher Gleason score (GS) with time from diagnostic biopsy. Initially, 20% of patients were intermediate risk, 0.3% high risk and all others low risk, and 31.2% of patients were upgraded during active surveillance. The proportion of patients upgraded increased with time, suggesting prostate cancer dedifferentiation occurred at a rate of 1.0%/year (95% CI, 0.12–2.16%/year). The estimated rate of increase was 2.5 times higher in patients with intermediate risk disease at diagnosis (rate 1.9%/year, 95% CI, 0.7–4.6) compared with those with low-risk disease (rate 0.75%/year, 95% CI, 0.5–2.0). Further analysis is underway. Among upgraded patients (n=114), 62% went on to have active treatment. Patients who were upgraded and treated had significantly greater prostate-specific antigen (PSA) velocities (median 1.2 ng/mL/y vs 0.42 ng/mL/y; p=0.01) and significantly higher Gleason scores when upgraded than those who remained on surveillance (21.8% vs 2.8% Gleason 8–10; p<0.01).

This is the largest rebiopsy cohort with long-term followup described to date, enabling the first estimates of prostate cancer dedifferentiation in patients on AS. Dedifferentiation rates appear higher in patients with intermediate-risk prostate cancer compared with those who are low risk at baseline.

IN BRIEF

Already known
• AS is effective at preventing overtreatment in men with prostate cancer.
• PSA velocity is predictive of disease progression.

What this study showed
• Pathologic upgrading is more common than in previous study reports.
• There was a relatively high rate of upgrading to a high-risk tier GS.
• Close surveillance is required for all men on AS.

Next steps
• Determine the importance of PSA kinetics in progression.
• Establish the optimal frequency of biopsies for men on AS.
9.2% developed GS 8 prostate cancer, while 5.4% developed GS 9 or greater. In multivariate analysis, risk factors for pathologic upgrading included a PSA velocity of >2ng/mL/yr (odds ratio [OR] 3.274; p<0.001), clinical stage of T2 (OR 2.577; p=0.0019), percentage of number of cores involved at diagnostic biopsy (OR 2.124; p<0.0001), and higher PSA at time of diagnosis (OR 1.578; p=0.0154).

The results presented show the highest rate of pathologic upgrading in an active surveillance cohort. Previous published studies revealed rates ranging from 2.5% at the University of Miami to 28% at Royal Marsden.1,2 The relatively high rate of upgrading, combined with the surprising upgrading of 14.6% to a high-risk tier of GS, highlights that all patients undergoing active surveillance require close followup. Although PSA velocity predicted progression in this cohort, the significance of PSA kinetics to predict pathologic upgrading is controversial. Data from UCSF and Johns Hopkins suggest that PSA kinetics do not correlate with pathologic progression, whereas studies of other large active surveillance cohorts, including Royal Marsden, showed that a PSA velocity of <2.0/year is predictive of disease progression.3,5

In conclusion, these results show that pathologic upgrading is common and that close surveillance is required. What is not known is the optimal method of followup: the significance of PSA kinetics, as well as the optimal frequency of prostate biopsies, are still uncertain.

References

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TRIAL SUMMARY: 20-year trend toward more non-bone metastases in mCRPC

BACKGROUND
Bone remains the most common site of metastasis in CRPC. With new therapies extending survival in metastatic CRPC (mCRPC), the authors hypothesized that the incidence of non-osseous metastases is increasing over time. In this study, they evaluated the pattern of metastatic disease in mCRPC as reported in baseline characteristics of prospective clinical trials over 2 decades.

All therapeutic studies in patients with mCRPC in PubMed and ASCO abstracts from 1990–2011 were identified. Inclusion criteria included phase II or III clinical trials in mCRPC with available baseline demographic data and no exclusion of specific site of metastatic disease (except brain). ASCO abstracts were limited to presentations in which data were available online. For each study, demographic data and study-reported sites of non-osseous metastatic disease were recorded (lymph node, visceral, soft tissue, liver). For each type of metastasis, weighted least-squares linear regression models were used to evaluate temporal trends.

FINDINGS
A total of 290 eligible studies (270 phase II and 20 phase III) were identified, involving 19,110 patients. Of these, 127 studies reported data on non-osseous metastases and prior chemotherapy. There was a significant trend over time (p=0.001) of increasing proportions of patients with non-osseous metastasis in both chemotherapy-naive and treated groups (1.4% per year increase). Increased lymph node, visceral and soft tissue metastases were seen over the study period. However, the proportion of patients with liver metastasis remained relatively stable.

The authors noted an increasing trend of non-osseous metastatic disease in patients with mCRPC over 20 years. This included lymph node, visceral and soft tissue metastatic disease, and this trend was observed in both chemotherapy-naive and treated patients. Longer survival and new therapies may be changing the clinical presentation of patients with mCRPC.

COMMENTARY: This study by Oh et al shows the possible pattern of change in the natural history of disease progression in patients with mCRPC that may be occurring over the last two decades with the development of novel therapeutics. Using a thorough search for phase II or III studies published in PubMed or presented at ASCO meetings, the investigators assessed the pattern of metastatic disease in 19,110 patients spanning 290 clinical trials. Interestingly, although 1947 trials were identified, most were excluded primarily due to duplication (presented at conference and published) or because the specific site of metastases was not identified. The authors used a weighted least-squares linear regression model to assess for significant temporal trends. The overall rate of non-osseous metastasis rose at a rate of 1.4% (p<0.001) and the greatest rise was between 2000–2011, in which it rose 2.8% per year (p<0.001). The greatest rise in non-osseous metastases was in lymph node spread (3.3% per year between 2000–2011; p<0.001) whereas no rise was seen in liver metastases during this time.

These results suggest that with the longer survival of
patients from novel systemic therapies, the development of non-osseous metastases is increasing. This may be due to the use of bone-targeted agents such as zoledronic acid and denosumab. The results of the study suggest that continued surveillance of non-osseous metastases is essential to determine disease progression. In addition, the possibility of a growing trend toward increased visceral metastases points to the need for continued development of non-bone specific targeted therapy for patients with mCRPC.

The investigators reported that the rise in non-osseous metastases was seen in both chemo-naive and chemotherapy-treated patients, implying that it may be due to the novel systemic therapies being tested in the clinical trial, rather than chemotherapy use itself or changing patterns of chemotherapy use.

The obvious limitation of the study is the lack of any standardization in the reporting of metastases in mCRPC trials, either in terms of the timing of testing or the reporting of progression itself. Furthermore, many patients were undoubtedly involved in many different clinical trials; hence, even though duplicate trials were removed, data from many patients may have been “duplicated” in the analysis. Regardless of these limitations, this study stresses that understanding the changing natural history of patients with mCRPC is crucial in the management of these patients, as well as in clinical trial development.

**LANDMARKS**

**IN BRIEF**

**Already known**
- New therapies have increased survival in CRPC over the past 20 years.
- Bone is the most common site of metastasis in CRPC, and novel therapies are now commonly used.

**What this study showed**
- There has been an increase in non-osseous metastases over the past 20 years, with the greatest rise occurring between 2000 and 2011.
- The rise was seen in chemo-naive and chemotherapy-treated patients.
- The rise may be associated with the use of novel therapies.

**Next steps**
- Pursue studies with standardized data on timing and site of metastases.
- Understand how the changing natural history of mCRPC should affect patient management and clinical trial development.