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Clinical Trials Deliver on the Promise of Science: What’s next?
Tomasz M. Beer, MD
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It began with observations that men with advanced prostate cancer that no longer responds to standard hormonal therapy can benefit from additional hormonal treatments. It was reinforced by laboratory discoveries that clearly showed prostate cancer cells do not become truly independent of male hormones. Almost always, quite the opposite happens.

(Continued on page 3)

Early Access for MDV3100 and Alpharadin (Radium-223 Chloride) UPDATE!
On behalf of the members of the newly formed Early Access for Prostate Cancer Patients volunteer committee that comprises advocacy leaders from different prostate cancer groups and health care professionals from around the US, we are pleased to announce that both Medivation/Astellas (makers of MDV3100) and Algeta/Bayer (makers of Alpharadin) are attempting to get their novel prostate cancer treatments to some doctors early through an Early Access Program (EAP) for patients that are running out of options! Please stay tuned because by the time this newsletter publishes we should have more information on the web site on when and where some patients can access these groundbreaking medications if they qualify. The fact that the producers of both of these drugs have already agreed to get their drugs out there early for some patients is an unprecedented moment in prostate cancer. We are grateful to both companies and will keep you posted, and the moment either drug becomes available early we will let you know immediately! BREAKING NEWS: Alpharadin (Radium-223) Now Available in New Orleans

Sincerely, Mark Moyad and Tom Kirk

Prostate Cancers Found on Serial Biopsy Often Clinically Insignificant
Most prostate cancers detected after more than two biopsies turn out to be clinically insignificant, a Cleveland Clinic study shows. “The risk of identifying clinically insignificant cancers appropriately tempers enthusiasm for serial biopsy,” comment Dr. Osama M. Zaytoun and colleagues.

They wrote online 15 March 2012 in the BJU International that most prostate cancers are detected on the initial biopsy or after one repeat biopsy, but “persistent suspicion of prostate cancer occasionally leads to serial biopsy.” However, the rate of detection declines with the number of repeat biopsies, and the clinical significance of detected cancers appears to decline also.

The team’s data are drawn from 479 men who underwent 749 repeat biopsies after two prior negative results. Biopsy protocols were either extended schemes involving 10-14 cores or saturation protocols of more than 20 cores. Cancer was detected eventually in 119 of the patients (24.8%), the investigators found, but 75 positive biopsies (63%) were for clinically insignificant cancer — i.e., a Gleason score <3, no more than 3 positive cores, and no more
COMPREHENSIVE REPORT ON PROSTATE CANCER MISCLASSIFICATION BY CURRENTLY USED LOW-RISK AND ACTIVE SURVEILLANCE CRITERIA


BJU Int, 7 February 2012
Epub ahead of print

Objective: To evaluate final histopathological features among men diagnosed with prostate cancer eligible for low-risk (LR) or active surveillance (AS) criteria.

Patients and Methods: We retrospectively applied 16 definitions for AS or LR prostate cancer to a contemporary (January 2008 to March 2011) open retropubic radical prostatectomy (RRP) series of 1745 patients. We excluded patients receiving neoadjuvant hormones or radiotherapy and those with inadequate histopathological reports and, <10 biopsy cores. Insignificant tumours were defined as ≤T2, Gleason score ≤6, tumour volume <0.5 mL and unfavourable tumour characteristics on final pathology was defined as extracapsular extension, seminal vesicle invasion, lymph node metastasis or Gleason upgrading. Sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV) were calculated.

Results: Eligibility of patients in the final study cohort (n= 1070) varied from 5.1% to 92.7% depending on the AS or LR criteria used. Final pathology revealed 77 insignificant cancers and 578 patients who had unfavourable histopathological criteria. The detection rate for insignificant cancers on final pathology was variable ranging from 7.8% to 28.3% depending on the AS- or LR-prediction tool used; unfavourable tumour characteristics were found in up to 33.5% on final pathology. The sensitivity, specificity, PPV and NPV were 8.5-97.9%, 24.7-97.8%, 67.7-89.1% and 45.3-78.2%, respectively. The likelihood ratio to correctly identify a patient with LR disease on final pathology ranged from 1.3 to 8.

Conclusions: AS or LR criteria have a significant risk of cancer misclassification. Better prediction tools are needed to improve these criteria. Re-biopsy might improve safety and should be considered more frequently in patients who opt for AS.

ASSOCIATION BETWEEN SMOKING STATUS AND FREE, TOTAL AND PERCENT FREE PROSTATE SPECIFIC ANTIGEN

Li J, Thompson T, Joseph DA, Master VA


Purpose: There are scant data available on the relationship between smoking and total prostate specific antigen (tPSA), free PSA (fPSA) and percent fPSA (%fPSA). Given the high prevalence of smoking and the frequency of PSA screening, it is important to determine any association between smoking and PSA values using nationally representative data.

Materials and Methods: Included in the final study population were 3,820 men 40 years old or older who participated in the 2001-2006 NHANES (National Health and Nutrition Examination Survey) and met the eligibility criteria for PSA testing. The distributions of tPSA, fPSA and %fPSA were estimated by sociodemographic and clinical characteristics. Multivariate linear regression models were fit to determine the adjusted relationship between smoking and tPSA and %fPSA while simultaneously controlling for these characteristics.

Results: For all ages combined fPSA levels were 0.90 (0.81-0.90) and 0.26 (0.25-0.28) ng/mL, respectively. Multivariate linear regression analysis showed that smoking was 7.9% and 12.2% lower among current and former smokers, respectively, than among never smokers. High body mass index and diabetes were also statistically significantly associated with a lower tPSA. Approximately a third of the men had a %PSA less than 25%. Current smokers had a significantly lower %PSA than former smokers.

Conclusions: Our finding that smoking is inversely associated with tPSA may have potential implications for the interpretation of PSA levels in men who are current or former smokers. Given the high prevalence of smoking, obesity and diabetes, additional research on the combined effect of these health risk factors is warranted.
When prostate cancer progresses on hormonal therapy it is because the cancer has found another way to activate its hormonal growth engine. Once the field understood that the hormonal system needed to be the focus of our attack, progress came rapidly. Spring of 2011 brought us the approval of abiraterone and in February of 2012, we learned that MDV-3100 extended life by 37% in men with very advanced prostate cancer! That is important progress, but we should be asking, “What’s next? Can we do better?”

The field is moving forward rapidly. There are a number of new drugs in early stages of development that target the hormonal system. The full potential of abiraterone and MDV-3100 has likely not yet been understood. In many cancers, effective cancer therapies have the greatest impact when they are deployed early in the course of the disease. Indeed, initial studies of abiraterone and MDV-3100 suggest that these drugs can stop prostate cancer from progressing for much longer when used before chemotherapy.

Phase III studies are under way and early reports suggest that abiraterone will be successful in this setting as well. Additional work will need to be done to determine if these agents can have an even bigger impact when used up front when hormonal therapy is just being started. Only when we have examined these drugs across the spectrum of prostate cancer, will we know their full potential.

Dr. Beer has been involved in more than 100 clinical trials and has led studies that tested new drugs in humans for the first time as well as large global studies that challenge the current standard of care. During the past year, Dr. Beer teamed up with Larry Axmaker, a cancer survivor and clinical trial participant to author a book entitled Cancer Clinical Trials, A Commonsense Guide to Experimental Cancer Therapies and Clinical Trials. Written for people living with cancer and their friends and families, the book demystifies the clinical research process, helps cancer patients decide if clinical trials are right for them, find and choose a clinical trial, and navigate and understand the experience of being a participant in clinical research.


(Continued on page 8)
Low oxygen levels in tumors can be used to predict cancer recurrence in men with intermediate-risk prostate cancer even before they receive radiation therapy (RT). The clinical research, led by radiation oncologists from the University of Toronto and the Princess Margaret Hospital (PMH) Cancer Program, University Health Network (UHN), was published online in Clinical Cancer Research, a journal of the American Association for Cancer Research.

“We’ve not only shown that men do worse if they have low oxygen levels (hypoxia) in their prostate cancer, but that they also do worse over a shorter period of time,” says Dr. Michael Milosevic, a U of T professor of radiation oncology and radiation oncologist in the PMH Cancer Program, UHN. “These patients seem to develop cancer recurrence within only a few years of completing treatment.”

Conclusions: Magnetic resonance imaging predicting reclassification were 83% (95% CI 73-93) and 81% (95% CI 71-91), respectively. PSA density was increased in patients with lesions larger than 1 cm on magnetic resonance imaging compared to those with no cancer on imaging (median 0.15 vs. 0.07 ng/ml/cc, p = 0.016).

Purpose: We report magnetic resonance imaging findings among unscreened men with low risk prostate cancer before active surveillance (AS).

Materials and Methods: We prospectively enrolled men with low grade, low risk, localized prostate cancer. All patients underwent multiparametric endorectal coil magnetic resonance imaging and were offered confirmatory biopsy within 1 year of imaging. The primary outcome was the impact of magnetic resonance imaging on identifying patients who were reclassified by confirmatory biopsy as no longer fulfilling AS criteria. We further identified clinical parameters associated with reclassification. The cohort was stratified as patients with (1) normal magnetic resonance imaging, (2) cancer on magnetic resonance imaging concordant with initial biopsy (less than 1 cm) and (3) cancer on magnetic resonance imaging larger than 1 cm. We performed univariate analysis to assess differences in clinical parameters among the groups.

Results: Magnetic resonance imaging did not detect cancer in 23 cases (38%) while magnetic resonance imaging and initial biopsy were concordant in 24 (40%). Magnetic resonance imaging detected a 1 cm or larger lesion in 13 patients (22%). Of the cases 18 (32.14%) were reclassified. When no cancer was identified on magnetic resonance imaging, only 2 cases (3.5%) were reclassified. The positive and negative predictive values for magnetic resonance imaging predicting reclassification were 83% (95% CI 73-93) and 81% (95% CI 71-91), respectively. PSA density was increased in patients with lesions larger than 1 cm on magnetic resonance imaging compared to those with no cancer on imaging (median 0.15 vs. 0.07 ng/ml/cc, p = 0.016).

Conclusions: Magnetic resonance imaging appears to have a high yield for predicting reclassification among men who elect active surveillance. Upon confirmation of our results magnetic resonance imaging may be used to better select and guide patients before AS.
Editors' note: Us TOO has invited certain physicians and others to provide information and commentary for the HotSheet to enrich its content to empower the reader. This column contains the opinions and thoughts of its author and is not necessarily those of Us TOO International.

Please explain the difference between extracapsular extension and positive margins when either is noted in the pathologists report after a radical prostatectomy. Does the risk of biochemical recurrence necessarily increase with either finding?

Actually, the terms are self-explanatory. Extracapsular extension means that the cancer has invaded through the capsule that surrounds the prostate gland and into the tissues surrounding the gland. Positive margins mean that cancer is seen to extend up to the cut edge of the surgical specimen. The presence of positive margins usually means the cancer is also extracapsular as it is standard for the surgeon to make the cut outside the prostate gland. Every so often, I see a case where positive margins were the result of the surgeon cutting through the prostate gland itself.

Both findings indicate an increased risk of recurrent prostate cancer. With positive margins, the risk is that some cancer remains behind after surgery on the other side of the cut the surgeon made. This is not always the case because in some patients the cauterization of the wound has destroyed the cancer at the margin. With extracapsular spread, the risk of recurrence is elevated for two reasons. First, the very fact that the cancer is invasive enough to invade through the capsule means that the cancer is quite aggressive. Second, extracapsular spread increases the chance that the cancer has invaded lymphatics and spread to lymph nodes or invaded blood vessels and spread into the blood stream.

Is adjuvant therapy indicated?

This is a controversial issue. I have seen a range of options offered at major prostate cancer centers. Some would radiate the prostate bed after surgery in such cases. Others would simply follow the PSA and radiate the prostate bed if the PSA starts to increase. A few centers would radiate the prostate bed and pelvic lymph nodes. The rationale for the latter is that prostate cancer commonly spreads to lymph nodes along the iliac and obturator lymph nodes.

Our recommendations depend on the aggressiveness of the disease. Most commonly, if the PSA is undetectable (less than 0.01 ng/mL), we will follow the PSA and consider treatment only if the PSA starts to elevate. Most recently, we have been sending patients with an elevating PSA to Sand Lake Imaging to get a Feraheme MRI to identify the location of the recurrent disease. This helps the radiation therapist tailor treatment to the individual patient’s pattern of relapse. If the PSA doubling time is greater than 9 months, we can often dramatically slow or arrest PSA progression with a program that also optimizes the patient’s general health. In these patients, we do not recommend adjuvant treatment.

If a post prostatectomy PSA reading is say <0.05 ng/mL, numerically what does this really mean? Is it for all practical purposes zero and not of concern or that it is 0.04 ng/mL something? Is it ever even possible to come in with a reading of 0.000?

These are very common questions and this reflects the inadequacies of mathematical training in the United States. The < symbol means “less than”. Thus, <0.05 ng/mL means that the actually PSA is less than 0.05 ng/mL. Time and again, I have patients trying to read more than this into such a result. Let me stress, this is really very simple: it only means one thing and that is that the actual PSA is less than 0.05 ng/mL. It might be 0.04, 0.01, 0.0008 or really any value less than 0.05 ng/mL.

The post prostatectomy PSA or ultrasensitive PSA test is standardized to go to 0.01 ng/mL, so the PSA test you are using, with a lower limit of 0.05, is not adequate. Both Quest and LabCorp have tests of appropriate sensitivity and we recommend patients use one of these two labs.

All PSA tests have a lower limit and the laboratory can only say that the actual value is below the lower limit of sensitivity of the assay they use. If you see a report of 0.00 ng/mL, indicating a zero PSA, then someone in the laboratory has fallen asleep on the job. Such a result is an impossibility.
IMPROVED CLINICAL OUTCOMES WITH HIGH DOSE IMAGE GUIDED RADIOTHERAPY COMPARED WITH NON-IGRT FOR THE TREATMENT OF CLINICALLY LOCALIZED PROSTATE CANCER


Int J Radiat Oncol Biol Phys 11 Feb 2012; Epub ahead of print

Purpose: To compare toxicity profiles and biochemical tumor control outcomes between patients treated with high-dose image-guided radiotherapy (IGRT) and high-dose intensity-modulated radiotherapy (IMRT) for clinically localized prostate cancer.

Materials and Methods: Between 2008 and 2009, 186 patients with prostate cancer were treated with IGRT to a dose of 86.4 Gy with daily correction of the target position based on kilovoltage imaging of implanted prostatic fiducial markers. This group of patients was retrospectively compared with a similar cohort of 190 patients who were treated between 2006 and 2007 with IMRT to the same prescription dose without, however, implanted fiducial markers in place (non-IGRT). The median follow-up time was 2.8 years (range, 2-6 years).

Results: A significant reduction in late urinary toxicity was observed for IGRT patients compared with the non-IGRT patients. The 3-year likelihood of grade 2 and higher urinary toxicity for the IGRT and non-IGRT cohorts were 10.4% and 20.0%, respectively (p = 0.02). Multivariate analysis identifying predictors for grade 2 or higher late urinary toxicity demonstrated that, in addition to the baseline International Prostate Symptom Score, IGRT was associated with significantly less late urinary toxicity compared with non-IGRT. The incidence of grade 2 and higher rectal toxicity was low for both treatment groups (1.0% and 1.6%, respectively; p = 0.81). No differences in PSA relapse.

(Continued on page 7)

DOC MOYAD’S WHAT WORKS & WHAT IS WORTHLESS COLUMN, ALSO KNOWN AS “NO BOGUS SCIENCE” COLUMN

“The Secret to a Long Life involves 7 different things and less than 2% of Americans follow them on a regular basis???”

Mark A. Moyad, MD, MPH
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Editors’ note: Us TOO has invited certain physicians and others to provide information and commentary for the HotSheet to enrich its content to empower the reader. This column contains the opinions and thoughts of its author and is not necessarily those of Us TOO International.

Bottom Line: The next time you get overly concerned about mercury in your fish please ask yourself if you are following these 7 healthy things because 98 to 99 out of every 100 Americans are currently not able to achieve them. That is wacky, but understandable.

Okay, here we go again? You know how I feel about everything from selenium supplements to the Ohio State Buckeyes (don’t tell anyone but I was actually cheering for them to win the NCAA basketball tournament after Michigan lost…I felt dirty…like I was cheating on my wife). Anyhow, here is this new United States study1 that shows that we can reduce the risk of dying from any cause by over 50%, and cardiovascular death by over 75% by following 6-7 healthy steps or parameters (compared to one or none) including:

- Not smoking
- Being physically active daily
- Having normal blood pressure
- Having normal blood glucose (sugar)
- Having normal cholesterol
- Maintaining normal weight for height
- Eating healthy

So, if you are overly concerned about high fructose corn syrup, bed bugs, or mercury in your vaccines….please go back to this Moyad master list because it will keep you centered on what really matters. I guess there is one positive thing about less than 2% of Americans that are not able to follow these changes, and that is that many doctors including myself would be out of work if most people did follow them (twisted thinking Dr Moyad…I know, but I like to look at the glass half empty once in while).

Reference:

GENE MAPPING NOT A CRYSTAL BALL FOR HEALTHY PEOPLE

New research suggests that for the average person, decoding ones DNA may not turn out to be a really useful crystal ball for future health.

Today, scientists map entire genomes mostly for research, as they study which genetic mutations play a role in different diseases. Or they use it to try to diagnose mystery illnesses that plague families. It’s different from getting a genetic test to see if you carry, say, a particular cancer-causing gene. But as genome mapping gets faster and cheaper, scientists and consumers have wondered if finding all glitches hidden in your DNA predict the diseases you’ll face decades later?

Johns Hopkins University developed a model using registries of thousands of identical twins, who despite their shared genes can develop different diseases.

They examined 24 ailments, including different cancers, heart disease, diabetes and Alzheimer’s. Under best-case scenarios, most people would be told they had a “somewhat” increased risk of at least one disease, says Bert Vogelstein, a Hopkins cancer geneticist and the study’s senior author.

But a negative test for most of the rest of the diseases doesn’t mean you won’t get them. It just means that you’re at no more risk than the general population.

Those are the findings Vogelstein’s team reported in the journal Science Translational Medicine. Why? Cancer, for example, typically doesn’t result from inherited genes but from mutations that can form anytime, Vogelstein explained.

(Continued on page 8)
a3p1c3 In a study with very important implications, Zaytoun and co-workers looked at men who had additional biopsies after two negative sets of biopsies had been performed. They found only 10% of 749 additional biopsies showed significant cancer in about one-fourth of the men. The factors that helped identify these men included ASAP and HGPIN. In their absence, the yield was very low.

THE BOTTOM LINE: Two negative biopsies may be adequate in most men unless either ASAP or HGPIN are found, in which case additional biopsies might be warranted.

a4p2c2 With clinicians increasingly acknowledging that prostate cancer is being over treated, active surveillance (AS) is becoming suggested more often. The challenge, however, is defining which patients are good candidates for this approach. The article by Palisaa and co-workers suggests that using various criteria, they only found 77 insignificant cancers out of over 1,070 patients who were thought to have low risk disease and underwent radical prostatectomy. This would mean that very few are really good candidates for AS. Something does not make sense here, however, as many experts believe that over treatment is occurring in closer to 50% of men. One of the characteristics they are using is a tumor volume <0.5 mL. Unfortunately, no information is available on the true natural history of this feature. Is this volume determined from a single tumor location or the total of all tumors in the specimen? One would expect that one tumor with that volume may pose more risk to a patient than 4 or 5 smaller tumors adding up to that amount. This has never been looked at but caution should be used at this time in applying this feature to defining if a patient is indeed a good candidate for AS.

a8p4c2 A second potential tool being looked at to identify AS candidates is MRI as reported by Margel and associates. They used tumors greater than 1 cm as being significant and this resulted in a positive and negative predictive value of 83 and 81%, respectively. The problem is that those numbers are probably not good enough to correctly identify enough patients at this time. Too many men are likely to be misclassified. However, perhaps this will improve with further work.

THE BOTTOM LINE: Although more work is needed to define who a good candidate for AS is, tumor volume in particular should be used with great caution as it appears to give misleading information.

a5p2c3 Over the years, several factors have been identified that may affect the serum PSA. In this issue of the HotSheet, an article found that smoking also affects the level by lowering it. This was true in current smokers and those that stopped in the past. This information might have been more important when doctors used an absolute cutoff of 3 or 4 ng/mL to tell a man that his PSA was abnormal and a biopsy was needed. However, now that we know no PSA level is normal, this information probably will not be very helpful in deciding who should have a prostate biopsy.

THE BOTTOM LINE: Although smoking may lower PSA levels, it really is not very useful information.

a10p6c1 Progress continues with radiation therapy for men with localized prostate cancer. Among ongoing questions is whether IGRT offers safer results than IMRT with comparable or better cancer control. The study by Zelensky and co-workers attempts to address that question and the results suggest better outcomes using the IGRT approach. However, several weaknesses in the study design make the conclusions suspect. For example, their study is retrospective and it compares men treated in 2008-09 to those treated in 2006-07. They also combine grade 2 toxicity, which is very mild, with grade 3 and higher, which is more troubling for patients.

THE BOTTOM LINE: Without a randomized study, the relative safety of IGRT compared to IMRT cannot be determined with sufficient accuracy to know if the technique should be preferred. In addition, using PSA to evaluate efficacy is not a satisfactory measure of cancer control.

a12p6c3 The study about gene mapping is another example of interesting information that offers little usefulness at this time. Knowing that someone has an increased chance of getting a certain disease does not provide a way to avoid that from happening, nor does it mean that it will actually occur. Also, as indicated in the article, not having a higher risk does not protect someone because it still may develop. So, for now, we can applaud the progress in the ability to map genes but much more is needed to find a way to use this information help to large numbers of people.

THE BOTTOM LINE: Gene mapping is another example of exciting progress in science but as yet it does not offer individuals a way to maintain or improve their health.

IGRT VS. NON-IGRT
(Continued from page 6)

free survival outcomes were observed for low- and intermediate-risk patients when treated with IGRT and non-IGRT. For high-risk patients, a significant improvement was observed at 3 years for patients treated with IGRT compared with non-IGRT.

Conclusions: IGRT is associated with an improvement in biochemical tumor control among high-risk patients and a lower rate of late urinary toxicity compared with high-dose IMRT. These data suggest that, for definitive RT, the placement of fiducial markers and daily tracking of target positioning may represent the preferred mode of EBRT delivery for the treatment of prostate cancer.
Many other common diseases are influenced by lifestyle and environment – so you’d still have to eat well, exercise and take the other usual precautions.

The study examined just one possible future use of genome mapping. It doesn’t mean there aren’t other benefits from the effort. This technology does have huge promise for customizing care for certain people, especially children with otherwise undiagnosed illnesses, says James Lupski of Baylor College of Medicine, who wasn’t involved in the study.

But even if finding a genetic explanation doesn’t lead to treatment, knowing whether it was inherited can help parents decide whether to chance having another baby, Lupski adds. “There are families where this can be transformative,” says Lupski. He had his own genome mapped to identify the cause of a rare nerve disorder.

Associated Press, 3 April 2012

than 50% cancer involvement in any positive core.

Dr. Zaytoun and colleagues conclude that the threshold for a repeat biopsy should be “very high” after more than one negative session, weighing the odds of detecting insignificant cancer against the risk of missing significant tumors.

“Patients with clear indication to consider serial biopsies are those with ASAP (atypical small acinar proliferation), or multifocal HPGIN (high-grade prostatic intraepithelial neoplasia) as part of a delayed interval biopsy protocol,” they advise.

On the other hand, “Patients with truly benign findings are strongly encouraged to forego future serial biopsy in the absence of significant changes in clinical suspicion, including changes in digital rectal exam, doubling of PSA level, or development of very low % fPSA (percentage free-total PSA).”

Reuters Health, 30 March 2012

650, 975, 1,300, 1,950 or 2,600 mg daily for 12 weeks. No man had received chemotherapy for his prostate cancer.

The maximum tolerated dose was not reached. Minor side effects included fatigue, nausea and diarrhea. Transient, nonserious elevated liver function tests were observed in 15 men, many of whom were asymptomatic. In early efficacy tests, 49% of men had ≥30% reductions in; 11 of whom had ≥50% reductions. In addition, tumor size decreased on CT scans in some patients.

“Because the androgen receptor controls PSA expression, improved PSA response shows that the drug is getting to the target,” said Montgomery. “For the majority of patients, to reduce their PSAs by 30 percent or more is quite good in a phase I dose-finding trial.”

AACR news release, 31 March 2012

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