INSIDE THIS ISSUE

US TOO® PROSTATE CANCER EDUCATION & SUPPORT

HOTSHEET

JANUARY 2014

NEW DRUG BOOSTS SURVIVAL IN PROSTATE CANCER

Men with advanced prostate cancer gained an extra 3 months of life with an investigational immunomodulator, including a 7-month survival improvement in men with bone metastases, a randomized trial showed. Tasquinimod treatment was associated with a median overall survival (OS) of 33 months compared with 30 months in placebo-treated men. The rate of disease progression was reduced by almost 50% in men receiving drug treatment. The difference in overall survival achieved statistical significance only in an adjusted analysis.

The immunomodulator was generally well-tolerated, and a biomarker analysis provided a few clues to tasquinimod's activity and the response to the agent, Andrew J. Armstrong, MD, of Duke University, and co-authors concluded in an article published online in the journal *Clinical Cancer Research*.

The growing number of therapies for metastatic prostate cancer has led to significant but incremental improvements in survival, generally on the order of 3–5 months. A need persists for novel therapies that can build on the survival benefits achieved with available therapies, the authors noted in their introduction.

Tasquinimod has anti-angiogenic, immunomodulatory, and anti-metastasis properties. Among other molecules, it targets S100A9, an immunomodulatory

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ONLY 11 SURGEONS RESPOND TO SURVEY ON DA VINCI SURGERY

During the past several years, a harsh spotlight has shone on the da Vinci robotic surgical system in the form of adverse events (AEs) reports filed with the government, academic studies, news stories, and dozens of lawsuits. Questions swirl around the technology's safety and cost-effectiveness.

The US Food and Drug Administration (FDA) released the results on November 8 of a survey of da Vinci surgeons earlier this year, undertaken to better understand the system's strengths and weaknesses. The responses were mostly positive and few in number – only 11 surgeons turned in answers. The FDA acknowledged that a "small convenience sample of respondents" was a limitation. The manufacturer of the robotic surgery system, Intuitive Surgical, agreed.

"While we are pleased with the surveyed surgeons' very positive observations about the benefits of robotic surgery, this small informal survey cannot serve as the basis for any scientifically valid conclusions," the company said in a statement issued to Medscape Medical News. It noted that "large clinical studies have documented the comparative benefits of robotic surgery."

The number of procedures done with the da Vinci Surgical System suggests a sizable cadre of da Vinci surgeons. First

(Continued on page 3)

TREATMENT OF PELVIC NODES INDIVIDUALIZED BY INCLUSION OF SENTINEL NODES IS FEASIBLE WITH IMRT

Treatment of pelvic nodes individualized by inclusion of sentinel nodes (SN) can be easily integrated into an IMRT-based treatment strategy, according to the new study conducted by a group of researchers from Tubingen and Munich in Germany. The target volume concept seems to correctly cover individual pelvic nodes, which is indicated by the absence of any nodal recurrence within five years of follow-up.

The results of the study were presented at the 5th European Multidisciplinary Meeting for Urological Cancer (EMUC in Marceille, France.

"Radiation treatment with long-term-androgen deprivation has level 1 evidence as treatment option for high risk prostate cancer patients," commented lead author of the study Dr. Arndt-Christian Müller of the Eberhard-Karls-Universität Tübingen.

"However, there is a discussion with regard to toxicity and efficacy concerning the inclusion of pelvic nodes into the radiation portals. With high conformal techniques such as IMRT for irradiation of pelvic lymph nodes, target volume contouring becomes highly important. There are standard lymph node radiation target volumes, yet the individual lymph

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INCIDENCE OF PROSTATE CANCER AFTER TERMINATION OF SCREENING IN A POPULATION-BASED RANDOMISED SCREENING TRIAL

Bergdahl AG, Holmberg E, Moss S, et al

Eur Urol 64:95-114, 2013

Background: In a previous publication from the Göteborg randomised screening trial, biennial PSA screening for men ≤69 yr of age was shown to lower prostate cancer (PCa) mortality by 44%. The evidence of the optimal age to stop screening, however, is limited.

Objective: To examine the risk of PCa after the discontinuation of screening.

Design, setting, and participants: In December 1994, 20 000 men in Göteborg, Sweden, between the ages of 50 and 65 yr were randomised to a screening arm (invited biennially to PSA testing) and a control arm (not invited). At the upper age limit (average: 69 yr), a total of 13 423 men (6449 and 6974 in the screening and control arms, respectively) were still alive without PCa. The incidence of PCa hereafter was established by matching with the Western Swedish Cancer Register. Participants were followed until a diagnosis of PCa, death, or final follow-up on June 30, 2012, or for a maximum of 12 yr after the last invitation.

Outcome measurements and statistical analysis: Incidence rates and disease-free survival were calculated with life table models, Kaplan-Meier estimates and a competing risk model.

Results and limitations: Postscreening, 173 cases of PCa were diagnosed in the screening arm (median follow-up: 4.8 yr) and 371 in the control arm (median follow-up: 4.9 yr). Up to 9 yr afterwards, all risk groups were more commonly diagnosed in the control arm, but after 9 yr the rates in the screening arm caught up, other than those for the low-risk group. PCa mortality also caught up after 9 yr.

Conclusions: Nine years after terminating PSA testing, the incidence of potentially lethal PCa equals that of non-screened men. Considering the high PCa mortality rate in men >80 yr of age, an age of 70 yr to discontinue screening might be too low. A flexible age to discontinue based on individual risk stratification should be recommended.

NO IMPROVEMENT NOTED IN OVERALL OR CAUSE-SPECIFIC SURVIVAL FOR MEN PRESENTING WITH METASTATIC PROSTATE CANCER OVER A 20-YEAR PERIOD

Wu JN, Fish KM, Evans CP, et al

Cancer 20 November 2013; Epub

Background: Prostate cancer mortality in the US has declined by nearly 40% over the last 25 years. However, to the authors' knowledge, the contribution of PSA screening for the early detection of prostate cancer remains unclear and controversial. In the current study, the authors attempted to determine whether improvements in survival over time among patients with metastatic prostate cancer (mPCa) have contributed to the decline in mortality.

Methods: Men aged ≥45 years who presented with de novo mPCa from 1988–2009 were identified in the California Cancer Registry. Overall survival (OS) and disease-specific survival (DSS) were estimated using the Kaplan-Meier method. Cox proportional hazards multivariate analysis models adjusted for different distributions of variables between groups were used .

Results: A total of 19,336 men presented with de novo metastatic prostate cancer during the study period. On multivariate analysis, OS was found to be better for men diagnosed from 1988–1992 and 1993–1998 than for men diagnosed in the most recent era (hazards ratio [HR], 0.78; 95% confidence interval [CI], 0.72-0.85 [P <0.001] and HR, 0.79; 95% CI, 0.74-0.86 [P <0.001]). There was no improvement in DSS observed when comparing the most contemporary men (those diagnosed from 2004–2009) with those diagnosed from 1988 –1997.

Conclusions: In this analysis of men presenting with de novo mPCa, no consistent improvement in OS or DSS could be demonstrated over time. These data suggest that improvements in survival for patients with advanced disease have not contributed substantially to the observed drop in prostate cancer mortality over the PSA era and that stage migration secondary to PSA screening plays a more prominent role.

DA VINCI SURVEY

(Continued from page 1)

approved by the FDA in 2000, the da Vinci Surgical System was used to perform some 367,000 procedures in the US last year, most of them gynecologic or urologic in nature, according to the company. There were 2042 da Vinci systems installed in US healthcare facilities as of September 30.

Six of the 11 surgeons who responded to the FDA survey practiced at healthcare institutions participating in the agency's Medical Product Safety Network (MedSun); the remaining surgeons were selected on the basis of referrals.

The FDA initiated the survey in January, after it saw a 34% spike in AE reports – including some involving injuries and death – filed with the FDA's Manufacturer and User Facility Device Experience database from 2011 to 2012. The number of da Vinci procedures during that period increased 26%. Mishaps on file include accidental electrical burns, severed nerves and blood vessels, and punctured bladders. Critics of the da Vinci Surgical System say such mistakes are happening in part because surgeons operating the robotic arms lack haptic feedback.

The FDA noted that the submission of an AE report does not necessarily mean that the device is faulty or defective. In addition, an increase in AE reports may simply reflect an increase in the number of procedures, publicity from product recalls, media coverage, and litigation.

The company came out on top in a well-publicized case in Washington State. A jury there found that Intuitive Surgical was not liable for the death of a man who underwent da Vinci–style prostate surgery. Lawyers for the man's estate failed to convince the jury that the company had not properly trained the surgeon to use its technology.

The FDA asked the surgeons about appropriate candidates for da Vinci surgery. Two urologists expressed worries about performing prostatectomies in obese men. For the lone cardiothoracic surgeon interviewed by the FDA, obesity was a common reason for turning patients down for coronary artery bypass surgery with this method.

Medscape Medical News, 11 November 2013

TASQUINIMOD SHOWS BENEFIT IN CRPC

(Continued from page 1)

protein expressed by myeloid-derived suppressor cells (MDSC). MDSCs are present in the tumor microenvironment, stimulate angiogenesis and immune tolerance. Studies demonstrated impaired tumor growth in S100A9 knockout models, suggesting S100A9 as a reasonable therapeutic target.

An international, phase II, randomized clinical trial showed that men treated with tasquinimod had significantly better 6-month progression-free survival (PFS, the primary endpoint) compared with placebo (69% vs. 37%, P=0.0001). In addition, the median PFS was two times longer in the tasquinimod group (7.6 vs. 3.3 months, P=0.0042).

Continuing the analysis of data from the randomized trial, Armstrong and colleagues reported findings from long-term follow-up and correlative biomarker studies, the latter being an exploratory analysis. The final analysis of the trial included 201 men with metastatic castration-resistant prostate cancer (mCRPC) that was minimally symptomatic or asymptomatic. They were randomized 2:1 to tasquinimod or placebo, and the results showed significant improvement in 6-month and overall PFS in the tasquinimod group.

The authors also reported data for OS, which was a secondary endpoint. An adjusted analysis of OS yielded a hazard ratio (HR) of 0.64, representing a 36% reduction in the hazard among men treated with tasquinimod (95% CI 0.42-0.97, P=0.034). Men with bone metastases at baseline appeared to derive greater benefit from tasquinimod, reflected in a median OS of 34.2 vs. 27.1 months in the placebo group, although the difference did not achieve statistical significance (HR 0.73, 95% CI 0.46-1.17).

During the open-label phase of the study, men in either treatment group could cross over to the opposite therapy. Subsequently, 41 (61%) of men in the placebo group were crossed over to tasquinimod. Men who crossed over lived 22 months longer than the men who decided against tasquinimod treatment, although the authors acknowledged that men who crossed over had more favorable prognostic characteristics.

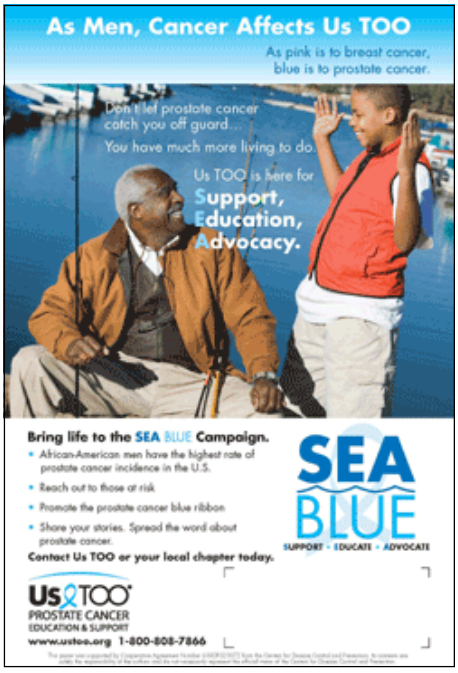
Biomarker analysis included markers known to be prognostic for mCRPC and markers relevant to tasquinimod's suggested antiangiogenic and immunomodulatory mechanism. Bone alkaline phosphatase and lactate dehydrogenase levels stabilized during tasquinimod treatment, but continued to increase during placebo treatment, suggesting a beneficial effect of tasquinimod on bone disease.

Baseline thrombospondin-1 levels below the median predicted improved OS with tasquinimod versus placebo. Baseline levels of all the other biomarkers evaluated had no predictive value.

"The current data suggest an overall favorable efficacy and safety profile for tasquinimod and not only justify its evaluation as a single agent in the pre-docetaxel phase III trial ... but also justify further combination studies with other active systemic therapies in men with castration-resistant prostate cancer," they concluded. "Tasquinimod's mechanism of action is not necessarily prostate cancer-specific and further evaluation in other tumor types is also warranted."

The authors pointed out that the true benefit of tasquinimod might have been obscured by a high rate of crossover from placebo to active therapy and by a chance imbalance in randomization that resulted in more men with visceral metastases in the tasquinimod arm.

MedPage Today, 21 November 2013



IMRT FOR LYMPH NODES

(Continued from page 1)

drainage of different patients is not taken into account."

According to the researchers, these new data on individual inclusion of sentinel nodes into the pelvic standard radiation target volumes with intensity modulated radiation therapy (IMRT) suggest that toxicity with advanced treatment techniques is low.

"With regard to efficacy, the absence of any nodal recurrence in the pelvis indicates that the sentinel node based target volume concept correctly covers individual pelvic lymph drainage," said Müller.

Regarding the risk profile in this series, such as high risk defined in one third by Gleason score 8-10, outcome parameters were at least comparable to available data of the same treatment period. Thus, this sentinel node-based approach justifies further evaluation including current dose-escalation strategies to the prostate in a larger prospective series.

"Firstly, we conclude that treatment of pelvic nodes individualized by inclusion of SN is feasible with IMRT. Secondly, the absence of any nodal pelvic recurrence within five years of follow-up indicates efficacy of this individualized treatment concept, summarised Müller.

"We expect an improvement of PSA control and with longer follow-up and higher patient numbers a survival benefit for patients with individual inclusion of sentinel lymph nodes".

According to the authors, the results of the study could be followed up by further evaluation of dose-escalated IMRT to prostate +/- SN-guided pelvic IMRT or treatment stratification after SN-biopsy with IMRT of prostate-only for node negative patients and IMRT of prostate +/- SN-guided IMRT in case of affected pelvic nodes.

Reference:

Müller A.-C. et al, Sentinel node based individualization of pelvic IMRT for high risk prostate cancer, 5th EMUC, Abstract 6.

Medical News Today, 19 November 2013

DOC MOYAD'S WHAT WORKS & WHAT IS WORTHLESS COLUMN, ALSO KNOWN AS "NO BOGUS SCIENCE" COLUMN

"Happy Holidays! Now go out there and tell your friends about MAGNESIUM and Michigan Football and why it was just a game in 2013?!"

Mark A. Moyad, MD, MPH, Univ. of Michigan Medical Center, Dept. of Urology

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:

Americans are getting too much of everything and obesity is a major epidemic as is taking too many antioxidant pills. However, most Americans are not getting enough potassium in their diets (mentioned in a prior Moyad column), nor are they getting enough magnesium. Recently, dietary magnesium was shown to be associated with a lower risk of cardiovascular disease (CVD) and may prevent a lot of health issues.[1]

What is more painful than losing to the Ohio State football team this year? NOTHING! We had them…all we needed was a successful 2-point conversion with less than 1 minute to go and then my life would have been complete! Perhaps, somewhat similar to the pain I felt after that game is the pain I feel when dietary magnesium is not touted or advertised to patients and health care professionals. Numerous popular drugs used by some prostate cancer patients can reduce blood magnesium levels including metformin and acid reflux drugs. Increasing levels of blood glucose and insulin can reduce magnesium as well as alcohol intake. And, there is now good evidence that lower intakes of dietary magnesium are associated with a greater risk of CVD and dying from CVD.

Magnesium also helps reduce the risk of constipation and kidney stones, which is why many calcium supplements now contain some magnesium. What is the impact of magnesium on prostate cancer? We have no idea, but the overall health benefits are so outstanding that everyone should know about this nutrient. The recommended dietary allowance (RDA) of magnesium is approximately 400-420 mg per day for adult men and 310-320 mg per day for adult women. Green leafy veggies such as spinach and higher fiber foods tend to contain more magnesium. For example, nuts such as almonds, seeds, and beans (soybeans…) are good sources. One of my favorite sources is the avocado because it is also high in potassium and healthy fat. Fish, brown rice, plain yogurt, and even bananas are also high in magnesium. So, you can take a magnesium supplement but keep in mind that primarily heart healthy foods are a good source of magnesium so it is best to stick with those food sources. Basically, magnesium is a forgotten nutrient today because it is not expensive and does not grab major headlines, but it has quietly become a major player in improving health and wellness.

So, similar to the Michigan football team that deserved to beat Ohio State in football, magnesium deserves more attention and respect! And, keep in mind that whenever my team loses I will respond now and forever by saying "it is just a game," but when we win I will respond by saying "it is more than a game." Oh, and I bet Auburn had higher blood levels of magnesium when they beat Alabama this year (hmm magnesium=the new legal steroid-like nutrient? I digress...).

Regardless, happy holidays and I hope you get more magnesium in your diet in 2014 and if you are really curious ask your doctor to pull your magnesium blood level next time you give blood because it will give you a good idea of how you are doing (it is an accurate test folks)!

Reference:

1. Del Gobbo LC, Imamura F, Wu JH, de Oliveira Otto MC, Chiuve SE, Mozaffarian D. Circulating and dietary magnesium and risk of cardiovascular disease: a systematic review and meta-analysis of prospective studies. Am J Clin Nutr 98:160-173, 2013.

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DOCTOR CHODAK'S BOTTOM LINE *(Ref Key: article #, page #, column #)*

Gerald Chodak, MD Author, Winning the Battle Against Prostate Cancer , Second Edition www.prostatevideos.com

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.

a1p1c1 The most important article in this month's HOT SHEET is about another new drug for advanced disease called Tasquinimod. It is thought to work by affecting the immune response and by affecting angiogenesis, which is the ability of tumors to stimulate the production of their own blood supply. A randomized phase II study in men with minimally symptomatic castrate resistant disease found that those taking this drug had a longer progression-free survival than men on placebo. A small increase in survival was also observed. This study prevents a strong conclusion about this drug; however, a phase III trial has been underway, which hopefully will show a similar benefit. If that does occur and the drug does get FDA approval, another new challenge will be to determine where this drug fits among the growing number of options for treating this group of patients.

The Bottom Line: Tasquinimod is another new non-chemotherapy agent with a novel mechanism action that appears to provide a benefit for men with castrate resistant metastatic disease. The results of the phase III trial will be anxiously awaited.

a3p1c3 The sentinel lymph node is thought to be the site of the first lymph node metastasis. Some studies suggest that if the sentinel node is negative, rarely are other nodes positive. Unfortunately, in prostate cancer, the sentinel node is often not removed during a standard or even extended lymph node dissection. It appears that if the sentinel node doesn't contain cancer cells, then other lymph nodes rarely contain cancer and they do not need to be removed or treated. However, if they do contain cancer then an extended dissection is needed or some cancer will go undetected. In the report by Muller, they evaluated delivering radiation to the sentinel node along with the other nodes being treated. It can be delivered with low toxicity. Based on their findings a prospective study may follow to determine if it affects long-term outcomes.

The Bottom Line: Preliminary data suggests low morbidity from delivering IMRT to sentinel nodes in intermediate and high-risk patients. Hopefully, a prospective, randomized study will follow to confirm these findings and determine if it will affect long-term survival.

a4p2c2 As more mature data appears on the long-term outcomes following randomized screening studies, doctors are trying to refine their recommendations to patients on when screening may no longer be warranted. Bergdahl and associates attempted to answer this question by looking at the national mortality from prostate cancer in men after a randomized screening study was discontinued. On the basis of the results, the authors suggest that an age of 70 may be too low to stop routine testing. Unfortunately, this is a theoretical paper with no prospective data assessing the impact of routine screening beyond age 70. For that reason, reliable conclusions are not possible.

The Bottom Line: Should men stop screening at age 70? That question was partly addressed in this study but the study design precludes making any firm conclusions.

a5p2c3 The article by Wu, et al attempts to argue that the drop observed in prostate cancer mortality in the last 25 years must be due to screening rather than improvements in treatment of advanced disease. The authors conducted a retrospective analysis of the California Cancer registry and divided the study into three periods. They found overall survival was better for men diagnosed between 1988 and 1998 compared to the next ten years. First of all the results make no sense. Not only has the death rate from non-cancer causes declined over that time, but also newer therapies for prostate cancer have been approved showing a longer survival time. The study makes no attempt to evaluate the treatments given to men over the various time periods. Without this knowledge it is possible that many of the men did not receive the latest therapies. Also, there may be a wide variability in the treatments delivered to men in each group. There is simply no way to make a valid assessment. This is yet another good example of how non-randomized, retrospective studies can deliver unreliable results.

The Bottom Line: This study does not make a valid argument that the drop in prostate cancer mortality over the last 25 years is due to screening rather than treatment.

a9p8c1 Is another cup of coffee good for you? That is the suggestion in the article by Discacciati et al who conducted a meta-analysis of published articles and identified eight reports assessing the impact of coffee consumption on high-risk disease and death from prostate cancer. They found a small reduction in high-grade and fatal disease. Unfortunately, none of the studies were randomized. For that reason, the reliability of the conclusion is difficult to assess. Once again, we are faced with all the reasons that non-randomized studies have potential biases that cannot be ignored unless a randomized study is done to confirm the observation. Some of the problems include how many years men drank their coffee, what was the age of the individuals when they started drinking coffee, what kind and how much sweetener they used and how was the tumor grade assessed. Was it from biopsy reports or was a special evaluation done to check and confirm the findings from the biopsy originally interpreted by different pathologists?

The Bottom Line: The benefit of coffee consumption on prostate cancer cannot reliably be assessed unless a randomized study is performed.

COFFEE CONSUMPTION AND RISK OF NONAGGRESSIVE, AGGRESSIVE AND FATAL PROSTATE CANCER – A DOSE-RESPONSE META-ANALYSIS

Discacciati A, Orsini N, Wolk A

Ann Oncol 24 November 2013; Epub

Background: Existing epidemiological evidence is controversial regarding the possible associations between coffee consumption and risk of prostate cancer by aggressiveness of the disease.

Materials and Methods: We conducted a random-effects dose-response meta-analysis to assess the relationships between coffee consumption and nonaggressive, aggressive and fatal prostate cancer risk. Studies were identified by a search of Medline and Embase databases to 15 July 2013. We carried out separate analyses by grade (Gleason score: low-grade, high-grade) and stage (TNM staging system: localized, advanced) of the tumors. Nonaggressive tumors were defined as low-grade or localized, while aggressive tumors were defined as high-grade or advanced.

Results: Eight studies (three case-control and five cohort) were included in this meta-analysis. Gleason 7 tumors were classified as high-grade in one study, while in another study, Gleason 7 (4 + 3) tumors were classified as high-grade and Gleason 7(3 + 4) as low-grade. In the remaining four studies, Gleason 7 tumors were excluded from the analyses or analyzed separately. The pooled relative risk (RR) for a consumption increment of 3 cups/day was 0.97 [95% confidence interval (CI) 0.92-1.03] for low-grade prostate cancer (n = 6), 0.97 (95% CI 0.94-0.99) for localized prostate cancer (n = 6), 0.89 (95% CI 0.78-1.00) for high-grade prostate cancer (n = 6), 0.95 (95% CI 0.85-1.06) for advanced prostate cancer (n = 6) and 0.89 (95% CI 0.82-0.97) for fatal prostate cancer (n = 4). No evidence of publication bias was observed. Heterogeneity was absent or marginal (I^2 range = 0-26%), with the only exception of the analysis on advanced prostate cancer, where moderate heterogeneity was observed (I^2 = 60%). When restricting the analyses only to those studies that defined high-grade tumors as Gleason 8-10, the inverse association became slightly stronger [RR: 0.84 (95% CI 0.72-0.98); n = 4].

Conclusions: Results from this dose-response meta-analysis suggest that coffee consumption may be inversely associated with the risk of fatal prostate cancer. No clear evidence of an association with PCa incidence was observed.

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