MAYO CLINIC

ClinicalUpdate

Current Trends in the Practice of Medicine

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INSIDE THIS ISSUE

FDA-Approved Imaging Modality Helps Locate Recurrent Prostate Cancers Early

The challenge

About 90,000 men annually seek treatment for recurrent prostate cancer, according to the Surveillance, Epidemiology and End Results Program. Biochemical recurrence (BCR) in men with prostate cancer undergoing definitive treatment is common, occurring in approximately 35 percent of men after radical prostatectomy and up to 40 percent of men after external beam radiation therapy. For this population, distinguishing focal from systemic disease recurrence is an important step. Patients with widely disseminated prostate cancer recurrence typically require systemic approaches to therapy. In patients with focal disease recurrence, however, anatomically targeted treatments may be an option.

Conventional imaging modalities such as CT scan, MRI and nuclear bone scan currently used in men with cancer recurrence are often insufficient for the detection of relapsing disease, particularly at prostate-specific antigen (PSA) levels below 5 nanograms per milliliter (ng/mL). Thus, current imaging modalities are less effective in guiding clinical management of patients with BCR.

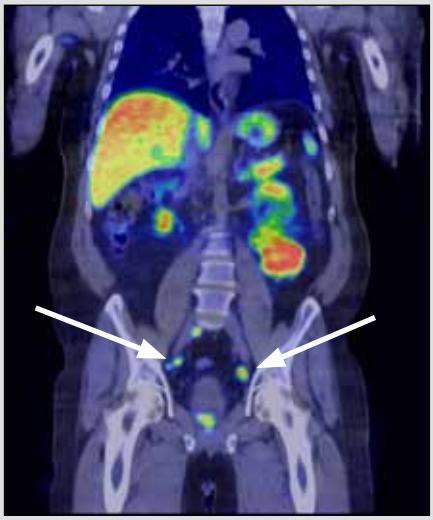

Figure 1. *Prostate cancer recurrence in the pelvis is seen on choline PET and CT scan (white arrows).*

Studying a new approach

Because it can reveal metabolically active and viable tumors, positron emission tomography (PET) with computerized tomography (CT) scan has recently emerged as a possible solution to this challenge. Recent research has identified 11C-choline as a suitable isotope. Choline is an essential component of phospholipids in the cell membrane. Choline kinase activity is up-regulated in tumor cells, including adenocarcinoma of the prostate. PET and CT scan with radiolabeled choline has shown promise for detecting the site of relapse in men with BCR after failed initial treatment.

Points to remember

- Conventional imaging modalities such as CT scan, MRI and nuclear bone scan currently used in men with prostate cancer recurrence are often insufficient for the detection of relapsing disease, particularly at prostate-specific antigen (PSA) levels below 5 nanograms per milliliter (ng/mL).
- Recent research has shown that positron emission tomography (PET) with computerized tomography (CT) scan with 11C-choline is a promising option for detecting the site of relapse in men with biochemical recurrence after failed initial treatment.
- Mayo Clinic researchers sought and received priority review and approval from the Food and Drug Administration (FDA) for the production and use of 11C-choline in patients with recurrent prostate cancer.

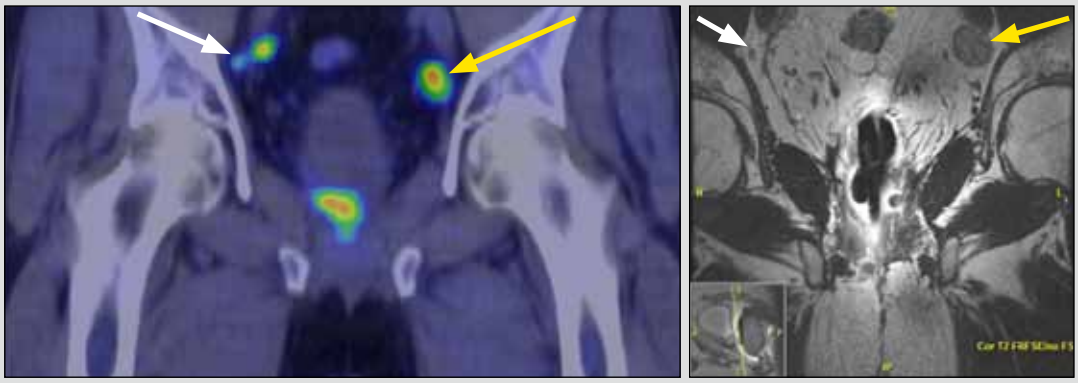

Figure 2. *Smallest sites of disease are not abnormal on MRI (white arrows). Larger ones are (yellow arrows).*

Mayo Clinic researchers recently evaluated the performance of 11C-choline PET and CT in detecting prostate cancer distribution and extent in men with BCR who have undergone one or more conventional imaging studies for the identification of recurrent prostate cancer. Performance was evaluated after their initial treatment.

In a retrospective review of all Mayo Clinic patients with prostate cancer who were evaluated using 11C-choline PET and CT from September 2007 to November 2010, Mayo analyzed the sensitivity, specificity, positive predictive value, negative predictive value and prostate-specific antigen threshold for the detection of recurrent lesions (Figures 1, 2 and 3).

Study results

The study period included 176 patients with BCR after primary treatment failure who underwent 11C-choline PET and CT. Using patient-based analysis, 11C-choline PET and CT yielded a sensitivity, specificity, positive predictive value and negative predictive value of 93 percent, 76 percent, 91 percent and 81 percent, respectively.

Of the 176 PET and CT scans performed, 56 (32 percent) prompted changes in clinical management. The optimal prostate-specific antigen level for prompting medical treatment changes after lesion detection was 2.0 ng/mL. On multivariate analysis, prostate-specific antigen level at PET (HR 1.37; $p = 0.04$) and clinical stage at initial diagnosis of prostate cancer (HR 5.19; $p = 0.0035$) were significant predictors of positive 11C-choline PET and CT.

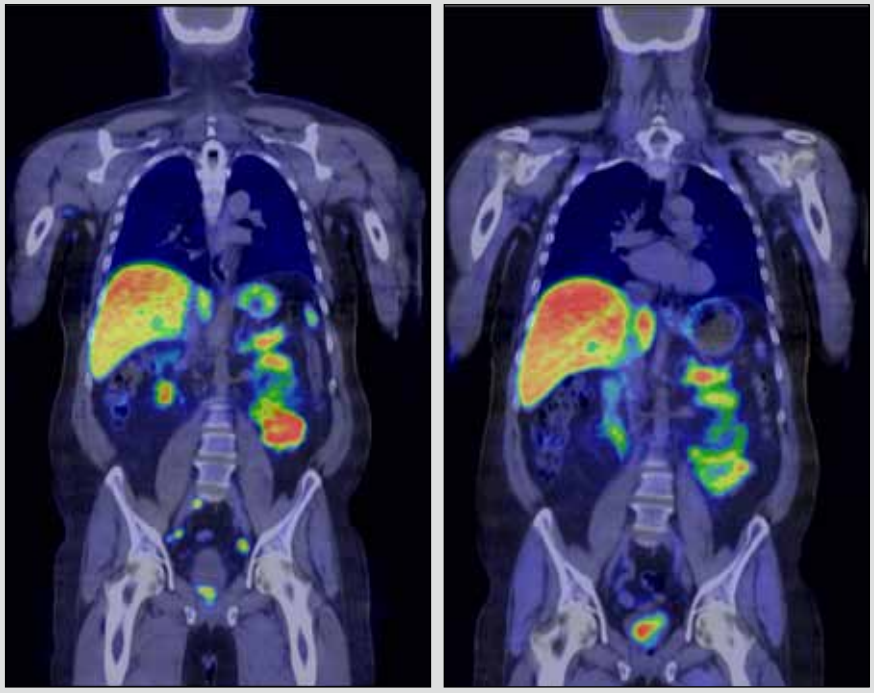

Figure 3. *Pre- and post-treatment of prostate cancer*

Conclusions

This study establishes that 11C-choline PET and CT performs well in men with biochemical recurrence after primary treatment failure. Mayo researchers believe that the ideal PSA range for optimal clinical effectiveness of 11C-choline PET and CT is likely between 1 and 2 ng/mL. which is lower than the purported effective range of many conventional imaging modalities. The Mayo team found that 11C-choline PET and CT substantially enhances the rate of prostate cancer lesion detection by approximately 32 percent beyond what can be garnered using conventional imaging techniques and at a lower prostate-specific antigen value.

FDA approval

Mayo Clinic researchers sought and received priority review and approval from the Food and Drug Administration for the production and use of 11C-choline in patients with biochemically recurrent prostate cancer in whom conventional imaging fails to identify recurrent disease. Within nine months of the researchers' application submission, Mayo Clinic became the first, and currently only, institution in North America approved to produce this imaging agent.

The next step: Medicare approval

Mayo physicians are actively consulting with Centers for Medicare & Medicaid Services contractors to get Medicare coverage for 11C-choline PET and CT when performed in men with biochemical recurrence with otherwise negative standard imaging. Coverage would provide access to the test for many men with prostate cancer who need it.

Mayo physicians hope to continue investigating the use of 11C-choline PET and CT to learn what treatments work best for the different forms of this disease and whether or not 11C-choline PET and CT can aid in treatment monitoring. The research team is also interested in developing the next generation of other radioisotopes to help pinpoint other types of cancers.

New Clinical Trial Evaluates Choice of Treatment for Left Main Coronary Disease

The development of the coronary artery bypass graft (CABG) in 1967 and percutaneous coronary interventions (PCIs) in 1977 were seminal events in the evolution of the treatment of coronary artery disease (CAD). Multiple clinical trials in the intervening years have helped clarify appropriate utilization of each approach. Meanwhile, improvements in anesthesia, operative technique and postoperative care, as well as technological advances in percutaneous systems, have resulted in reduced hospital stays and improved outcomes and durability for both procedures. These advances, however, challenge the medical community to continually re-evaluate the safety, efficacy and indications for these treatment modalities.

Traditionally, individuals with significant stenosis of the left main (LM) coronary artery were treated with a CABG rather than PCI due to the large area of myocardium at risk, the dire consequences of abrupt periprocedural closure and concerns regarding durability of PCI. The introduction of drug-eluting stents, and now second-generation drug-eluting stents, has prompted re-examination of the possible role of PCI for some patients with LM disease. There is now evidence to suggest that PCI with drug-eluting stents may be appropriate treatment for some patients with LM disease, especially when the total burden of coronary disease is not high.

Although the Synergy Between PCI With TAXUS and Cardiac Surgery (SYNTAX) randomized trial found that PCI with the first generation of paclitaxel-eluting stents in patients with three-vessel and LM disease was inferior to CABG — for the composite primary

Points to remember

- Until recently, individuals with significant stenosis of the left main (LM) coronary artery were treated with coronary artery bypass grafting rather than percutaneous coronary interventions (PCIs).
- The introduction of drug-eluting stents has prompted re-examination of the possible role of PCI for some patients with LM coronary artery disease.
- Mayo Clinic recently participated in a major clinical trial (EXCEL) to evaluate second-generation drug-eluting stents versus coronary artery bypass surgery for revascularization of the LM coronary artery. The EXCEL trial will clarify the role of second-generation drug-eluting stents for treating LM coronary artery disease.

endpoint of death, myocardial infarction (MI), stroke or revascularization at one year — a post hoc analysis suggested that subgroups with low anatomic SYNTAX scores had similar outcomes with PCI compared with CABG.

Second-generation drug-eluting stents have been shown to demonstrate lower restenosis and stent thrombosis rates than do first-generation stents. A Trial of Everolimus-Eluting Stents and Paclitaxel-Eluting Stents for Coronary Revascularization in Daily Practice: The COMPARE Trial (COMPARE 1) was a single-center, real-world prospective randomized study conducted in the Netherlands comparing the clinical performance of paclitaxel- and everolimus-eluting stents. The rate of major adverse events (all death, nonfatal MI and target vessel revascularization) was significantly higher in the paclitaxel group than in the everolimus group at one year (9.1 percent vs. 6.2 percent; p = 0.023) and two years (13.7 percent vs. 9.0 percent; p = 0.0016). The everolimus group also had lower rates of stent thrombosis at one year (2.6 percent vs. 0.7 percent; p = 0.002) and two years (3.9 percent vs. 0.9 percent; p = 0.0001), primarily due to a reduction in early stent thrombosis. However, only 2 percent of the patients in this trial had unprotected LM stenting.

Mayo Clinic in Rochester, Minn., recently participated in the Evaluation of XIENCE PRIME™ Everolimus-Eluting Stent System (EECSS) or XIENCE V® EECSS or XIENCE Xpedition™ EECSS or XIENCE PRO EECSS Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (EXCEL) clinical trial. This trial will clarify the role of second-generation drug-eluting stents for LM disease. Results of the trial endpoints — composite all-cause mortality, MI, cerebrovascular accident (CVA) at three years — will be reported in 2016.

The EXCEL trial randomized 2,600 patients at 165 sites globally; 1,300 received stenting and 1,300 underwent CABG. Inclusion and exclusion criteria are outlined in Box 1 and Box 2. In addition to clinical endpoints (Box 3), the study evaluated quality-of-life scores and analyzed procedural and follow-up costs for the full study period. Please watch future issues of *Clinical Update* for information about findings from the EXCEL trial.

Box 1. EXCEL trial main inclusion criteria

- Unprotected LM coronary artery disease with angiographic stenosis ≥ 70 percent requiring revascularization as assessed by both interventional cardiologist and cardiac surgeon

or

- Unprotected LM coronary artery disease with angiographic stenosis ≥ 50 percent but < 70 percent requiring revascularization as assessed by both interventional cardiologist and cardiac surgeon and one of the following:
  - Noninvasive evidence of ischemia referable to an LM lesion
  - Intravascular ultrasound (IVUS) minimal luminal area (MLA) ≤ 6.0 mm^2
  - Fractional flow reserve (FFR) ≤ 0.80

or

- Significant LM equivalent disease: ostial lesions of left anterior descending (LAD) and circumflex artery (CFX) ≥ 70 percent

or

- One or both of the ostial LAD and CFX lesions ≥ 50 percent and < 70 percent and one of the following:
  - Noninvasive evidence of ischemia
  - IVUS MLA ≤ 4.0 mm^2
  - FFR ≤ 0.80
- Clinical and anatomic eligibility for both PCI and CABG
- Silent ischemia, stable angina, unstable angina or recent MI

Box 2. EXCEL trial main exclusion criteria

- Prior PCI LM at any time
- Prior CABG at any time
- Prior PCI on any coronary artery within past year
- Need for other cardiac surgery
- Need for any other surgery within the next year
- Inability to tolerate dual anti-platelet therapy for at least one year
- Noncardiac comorbidities with life expectancy of ≤ three years
- Other investigational studies
- Pregnancy

Box 3. EXCEL trial endpoints

Primary endpoint

- Composite all-cause mortality, MI, CVA at three years

Secondary endpoints

- All-cause mortality, MI, CVA at 30 days
- Unplanned revascularization within three years
- Quality-of-life measures and treatment costs for the full follow-up period

Movement Disorder Laboratory Diagnoses and Treats Complex Dystonias

Movement disorders such as tremor, dystonia and Parkinson's disease are among the most common neurological conditions. For patients, movement disorders can result in considerable disability. Hand and arm tremor can impair eating, handwriting and grooming. Vocal tremor can hinder communication, resulting in social withdrawal. For the physician, precise diagnosis can be difficult because of the broad array of related movement disorders.

Mayo Clinic Movement Disorder Laboratory in Rochester, Minn., is one of the few centers in the United States that offers a wide range of analytic techniques capable of aiding in the classification of these conditions. Among the techniques used are tremor-frequency analysis, quantitative brain wave analysis, dystonia mapping studies and movement-pattern analysis. The core assessment tool comprises simultaneous electroencephalogram (EEG), electromyogram (EMG) and video recordings taken while the patient exhibits abnormal movements.

Although most EMG laboratories focus on disorders of the peripheral nervous system, Mayo Clinic's laboratory also uses these techniques to diagnose problems of the central nervous system. A typical diagnostic test in the Movement Disorder Laboratory lasts 20 to 45 minutes. Surface EMG is used to monitor muscle activity. For some conditions, such as myoclonus, EEG helps determine the locus of abnormal movement in the central nervous system. Computer analysis of the recordings has advantages for diagnostic specificity, often allowing identification of the precise type of tremor a patient has.

Points to remember

- Although most electromyogram (EMG) laboratories focus on disorders of the peripheral nervous system, Mayo Clinic's laboratory also uses multiple techniques to diagnose and classify movement disorder problems of the central nervous system precisely.
- Among the techniques used are tremor-frequency analysis, quantitative brain wave analysis, dystonia mapping studies and movement-pattern analysis. The core assessment tool comprises simultaneous electroencephalogram (EEG), EMG and video recordings taken while the patient exhibits abnormal movements.

Stiff person syndrome

The experience and expertise of Mayo's movement specialists extend to rare movement disorders, such as orthostatic tremor and stiff man syndrome (SMS), also known as stiff person syndrome. Two-thirds of patients who received a diagnosis of this rare disorder at Mayo during the period from 1984 through December 2008 were women.

SMS, identified by Mayo Clinic in 1956, is characterized by chronic rigidity and spasms in the muscles of the limbs and trunk. Patients frequently have painful spasms and falls, as well as fixed spinal deformities from long-term rigidity. Some patients have respiratory impairment from chest wall spasms.

SMS is distinguishable by hyperexcitability of spinal motor neurons. Mayo Clinic Movement Disorder Laboratory uses multichannel surface EMG, concentric needle studies of the lumbar paraspinal muscles, and electrical and acoustic stimulation of the nerves to evaluate startle reflexes in suspected cases of SMS. This condition is often mistaken for a psychogenic disorder, but electrophysiological findings consistent with brainstem and spinal hyperexcitability can help confirm the clinical suspicion in many cases.

Diagnostic testing in the Movement Disorder Laboratory can also guide treatment. For example, multichannel EMG needle mapping studies can pinpoint areas of activity that cause spasmodic torticollis. Precise localization can then help physicians choose sites for injecting botulinum toxin and identify patients who might benefit from surgical treatment.

Collaborative care for complex conditions

Mayo also has a large practice in treating spasmodic dysphonia and jaw and orofacial dystonias with botulinum toxin. Movement disorders neurologists, ear, nose and throat surgeons, and speech pathologists share a close collaboration in caring for patients who receive these complex injections.

Movement disorders, particularly in rare conditions, can be very difficult to diagnose and treat. The expertise at Mayo Clinic lies in clarifying a difficult diagnosis, as well as providing botulinum toxin treatment in common and rare conditions.

Patellofemoral Arthroplasty in Patients With Arthritis

For more than a decade, good to excellent results have been obtained in patients with patellofemoral arthritis (PFA) who have undergone total knee arthroplasty (TKA) to relieve debilitating pain and impaired mobility. Still, there is controversy over the optimal surgical management of these patients. The central question persists: Is TKA more than is needed to restore pain-free mobility — especially in young, active patients?

A new approach

The vast majority of patellofemoral pain and early patellofemoral arthritis can and should be treated nonoperatively. But cautious consideration of a new approach, patellofemoral arthroplasty (PFA), may be indicated in carefully selected refractory cases of advanced degenerative disease confined to the patellofemoral articulation (Figure 1).

Points to remember

- The vast majority of patellofemoral pain and early patellofemoral arthritis can and should be treated nonoperatively.
- A new approach, patellofemoral arthroplasty (PFA), however, may be indicated in carefully selected refractory cases of advanced degenerative disease confined to the patellofemoral articulation.
- Patient selection is central to the success of treating patellofemoral arthritis with PFA.

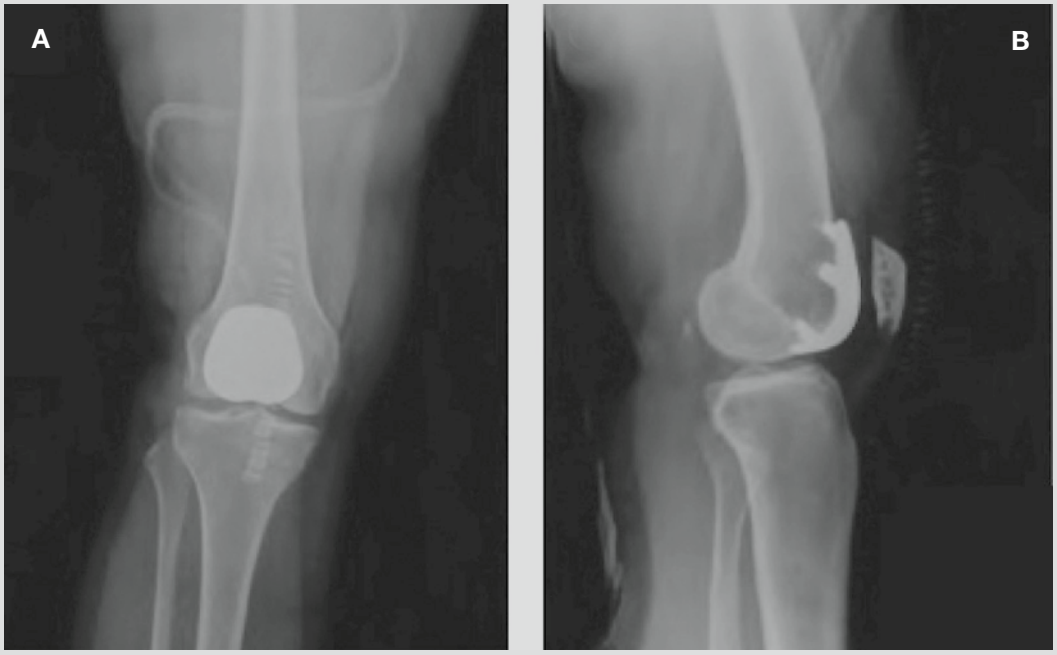

Figure 1. *Postoperative radiographs of (A) anterior-posterior and (B) lateral views of patellofemoral arthroplasty.* Printed with permission. *Orthopedic Update*, 2012.

Patients with patellofemoral arthritis may not have disease in all three knee compartments. This finding has led a few centers — Mayo Clinic among them — to adapt partial knee arthroplasty approaches more commonly used in lateral and medial compartment procedures to cases involving only the patellofemoral articulation. Although the study of the technique is ongoing, Mayo surgeons have performed more than 100 procedures and are encouraged by the early results. Selecting the appropriate patient is paramount to achieving the goal of excellent outcomes associated with TKA, but through a less invasive surgical procedure (Figure 2).

Benefits and risks

Compared with TKA, partial, or unicompartmental, arthroplasty management of isolated patellofemoral arthritis offers potential benefits of:

- Sparing the remaining healthy knee compartments and associated structures
- Inflicting less surgical trauma and blood loss

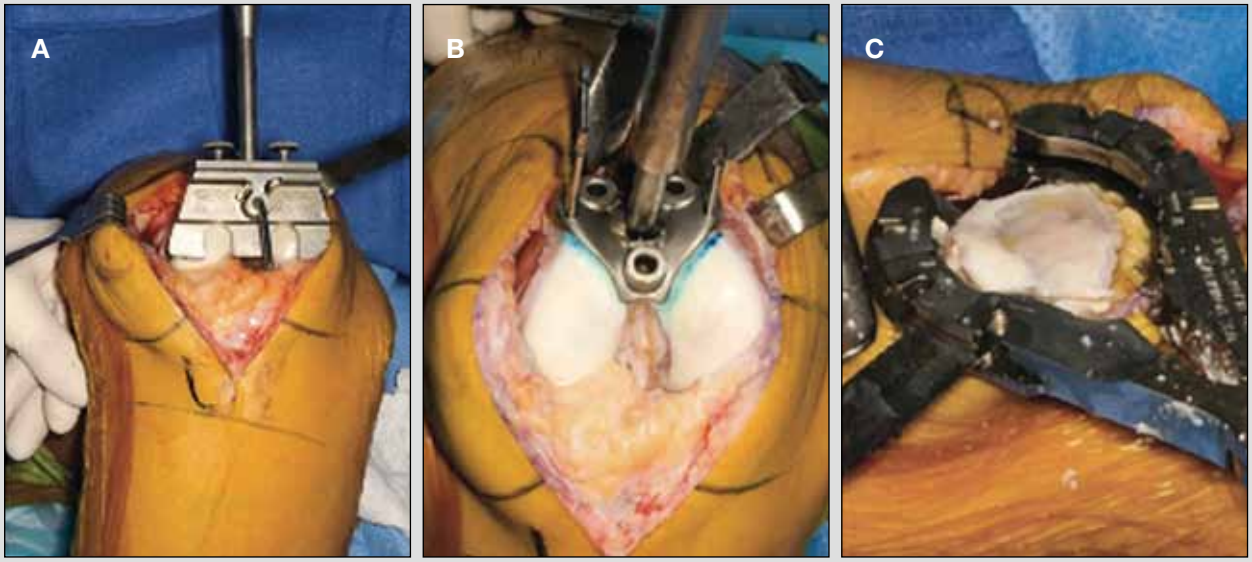

Figure 2. *(A) PFA technique involves an anterior femoral cut to initiate the procedure, as seen here. (B) The trochlea is prepared. (C) The patella is prepared.* Printed with permission. *Orthopedic Update*, 2012.

- Minimizing risk of complications
- Reducing hospital stay
- Supporting an easier overall recovery and return to lifestyle
- Possibly serving as a bridging treatment for active younger patients who may one day be candidates for TKA

Risks include mid- to long-term failure as a result of tibiofemoral degeneration, which has been reported to occur in up to 25 percent of patients and is the subject of a new Mayo Clinic study.

Identifying the ideal patient for PFA

Patient selection is central to the success of treating patellofemoral arthritis with the partial procedure. Patellofemoral pain is multifactorial and complex in terms of symptomatology, and patients may be motivated by their discomfort and disability to assume the solution is surgical. But it is imperative to exhaust all nonoperative measures first. Surgery is not indicated for mild cases that upon radiographic, MRI or arthroscopic exam lack severe degeneration of the patellofemoral articulation.

In addition to fulfilling indication criteria (Table), the ideal patient also has the following features:

- Minimal pain while walking on level surfaces
- Isolated anterior retropatellar pain that is exacerbated by:
  - Standing from seated position
  - Climbing up and down stairs
  - Walking on uneven surfaces
  - Sitting long periods with knee flexed

Table. Patient selection criteria.

Indications	Contraindications
Advanced, isolated primary PFA	Moderate or advanced tibiofemoral chondromalacia
PFA with trochlear dysplasia, often with a history of instability	Severe malalignment/malt racking
Post-traumatic PFA	Inflammatory arthritis, morbid obesity, patella baja

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Mayo Clinic
Clinical Update

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25th Annual Clinical Reviews — A Family Medicine and Internal Medicine Update
March 26-29, 2014, in Scottsdale, Ariz.
Four-day review features medical updates and management strategies for various diseases via lectures, Q&A panel discussions, a unique interactive format that allows for immediate audience participation, breakout sessions and Meet the Preceptor luncheons for one-on-one interaction with faculty. For more information or to register, call 480-301-4580, email *mca.cme@mayo.edu or visit www.mayo.edu/cme.*

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