Review Article

Percutaneous Interventional Therapy for Chronic Thromboembolic Pulmonary Hypertension

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ABSTRACT

Chronic thromboembolic pulmonary hypertension is a form of precapillary pulmonary hypertension resulting from the incomplete resolution of pulmonary thromboemboli and formation of chronic, fibrotic, flow-limiting obstructions within the pulmonary vasculature. The progression of chronic thromboembolic disease is associated with the development of pulmonary hypertension, right heart failure, and diminished patient function. Surgical pulmonary thromboendarterectomy to extract thromboembolic disease is curative and the primary treatment option for chronic thromboembolic pulmonary hypertension. For patients who are not surgical candidates, balloon pulmonary angioplasty (BPA) is a percutaneous treatment option that uses angioplasty techniques to dilate diseased pulmonary arteries, disrupt organized flow-limiting obstructions, revascularize underperfused lung regions, improve pulmonary vascular hemodynamics, and restore patient function. BPA has undergone refinement and worldwide adoption since its inception, leading to advancements in the equipment used, technical approach, and complication management for each procedure. The approach to modern BPA, its attendant complications, and contemporary treatment outcomes are discussed in this state-of-the-art review.

ABBREVIATIONS

6MWD, 6-minute walk distance; BPA, balloon pulmonary angioplasty; CBCT, cone beam computed tomography; CTEPH, chronic thromboembolic pulmonary hypertension; IVUS, intravascular ultrasound; OCT, optical coherence tomography; PTE, pulmonary thromboendarterectomy; RPE, reperfusion pulmonary edema.

Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is a form of precapillary pulmonary hypertension that results from the incomplete resolution of pulmonary thromboemboli and the subsequent formation of chronic, fibrotic, flow-limiting obstructions within the pulmonary vasculature (Figure 1). The persistence and progression of chronic thromboembolic disease are associated with the development of pulmonary hypertension, right heart failure, and diminished patient function. The extraction of thromboembolic disease via surgical pulmonary thromboendarterectomy (PTE) is potentially curative and remains the primary treatment option for CTEPH patients. For CTEPH patients who are not surgical candidates, balloon pulmonary angioplasty (BPA) is a percutaneous treatment option that uses angioplasty techniques to dilate narrowed or occluded pulmonary arteries, thereby disrupting organized flow-limiting obstructions, revascularizing underperfused lung regions, improving pulmonary vascular hemodynamics, and restoring patient function. The BPA procedure has undergone continuous refinement and worldwide adoption since being first performed in 1986, leading to advancements in the equipment used, technical approach, and complication management for each procedure. Contemporary BPA has an important and expanding role in treating patients who are technically inoperable, have an unfavorable surgical risk–benefit ratio, or have persistent or recurrent pulmonary hypertension (PH) after PTE.

Approach to Balloon Pulmonary Angioplasty

Patient Selection for Balloon Pulmonary Angioplasty

The identification of patients best suited for BPA therapy is performed by a multidisciplinary team consisting of interventional cardiologists, PTE surgical experts, and pulmonary vascular medicine specialists who are highly experienced in evaluating patients with CTEPH. Determination of surgical inoperability can be controversial and is highly
dependent on local surgical expertise, proximal vs. distal pulmonary segmental disease, patient comorbidities, and patient preference. The majority of BPA procedures are performed in patients who have symptomatic, inoperable CTEPH or persistent/recurrent pulmonary hypertension following PTE. “Rescue” BPA has been described as a palliative treatment option for patients with rapidly deteriorating CTEPH prior to PTE. “Hybrid” BPA in combination with PTE has also been described for select CTEPH patients with surgically accessible disease in one lung and inoperable disease in the contralateral lung.

General Treatment Strategy

Although there is no standardized technique for how BPA is performed, we describe the approach developed at UC San Diego and adapted from the shared experiences of BPA operators worldwide (Table 1). A complete BPA treatment course usually involves 4 to 6 separate BPA procedures, each spaced apart by 3 to 7 days, and concluded by one final BPA treatment procedure for the right lung as well as for the left lung. Noninvasive perfusion scans are used to identify the lung areas with the largest perfusion defects and the target vessels for BPA revascularization. Perfusion scanning is intermittently repeated to observe overall changes in lung perfusion from baseline and guide subsequent BPA treatments. Baseline and interval 6-minute walk distances (6MWDs) are measured to follow clinical response to BPA, while right heart catheterization before each BPA session surrelves the cumulative hemodynamic response to BPA. Each BPA procedure is also limited to the treatment of a single lung, as well as 2 Gray radiation dose and 400 ml of administered contrast.

Vascular Access

The BPA procedure begins with ultrasound-guided femoral vein access and insertion of a 9-French vascular introducer sheath. At UC San Diego, we adopted the routine use of femoral venous access as the preferred access for BPA, rather than the internal jugular or brachial vein, due to ease-of-use and lower radiation exposure for operators. After right heart catheterization is performed, a single-lumen wedge catheter is directed into the target lung and exchanged over a 0.035-inch guidewire for a 90-cm 6-French sheath, which is then advanced until positioned just beyond the pulmonary artery bifurcation.

Segmental Pulmonary Angiography

A preshaped 6-French guide catheter is introduced into the 6-French sheath, carefully advanced over a stiff angled Glidewire (Terumo Corporation, Tokyo, Japan), and directed toward the pulmonary lobe of interest. The majority of BPA procedures are performed using a Judkins-right or Multipurpose guide catheter, which can be manipulated to engage various pulmonary artery segments. Selective segmental pulmonary angiograms provide valuable information regarding target vessel size, target lesion characteristics, distal pulmonary artery flow, and pulmonary venous drainage before, and following, BPA therapy. Selective angiograms can also be used to identify the presence and location of pulmonary vascular injury during BPA. Selective angiograms are acquired using a patient’s deep breath hold, 1:1 diluted contrast for injection, and a frame rate of 7.5 to 15 frames/s without digital subtraction. While angiograms using higher radiation doses, higher frame rates and biplanar imaging can help with detailed lesion characterization, we have exclusively shifted to lower dose single-plane angiography to minimize patient radiation dose and operator exposure. No compromise in clinical or technical success has occurred as a result of these changes.
Target Lesion Characterization

Typical angiographic characteristics of fibrotic thromboembolic pulmonary artery disease include the appearance of webs, bands, intimal irregularities, pouch defects, abrupt vascular narrowing, and complete vessel occlusion (Figure 1). Other contemporary imaging modalities, including intravascular ultrasound (IVUS), optical coherence tomography (OCT), and cone beam computed tomography (CBCT), have also been used for adjunctive CTEPH lesion characterization and BPA guidance.

OCT was first utilized for CTEPH lesion characterization in 2010 and revealed the presence of intraluminal flaps and occlusions with overlying thrombus. Subsequent OCT use has demonstrated a diversity of CTEPH lesion characteristics ranging from classic fibrotic circumferential bands, fenestrated occlusions, and intraluminal fibrotic stands of varying thickness and organization within weblike or abruptly narrowed lesions. While the resolution and potential image clarity of OCT are superior to IVUS for lesion characterization and vessel sizing during BPA, OCT is not routinely utilized due to safety and resource utilization concerns with additional robust injections of undiluted contrast needed for optimal imaging. IVUS imaging can be safely performed to characterize chronic thromboembolic lesions and evaluate the size of distal pulmonary arteries without additional contrast injections. IVUS virtual histology, analyzing reflected ultrasound signals from surrounding arterial structures, has been used during BPA to identify lumen-occupying thrombi, analyze target pulmonary arteries for balloon dilation, and guide balloon catheter sizing. Fibrous tissue identified by IVUS virtual histology was also found to be more compressible and responsive to BPA therapy compared to tissue categorized as having a necrotic core or dense calcification. High-resolution segmental and subsegmental pulmonary angiography using CBCT has also been used to evaluate and classify distal CTEPH lesions (type 1: webs, type 2: web and slits, type 3: slits, and type 4: narrowing or complete occlusion). The category of web and slits was found to be the most common type of distal CTEPH disease by CBCT. Despite the availability of these multiple high-resolution imaging modalities to characterize CTEPH target lesions, segmental pulmonary angiography during BPA remains the primary mode of identifying optimal targets for balloon dilation.

Pulmonary Artery Intervention

The aim of BPA is to disrupt organized, flow-limiting obstructions and improve pulmonary vascular blood flow while avoiding complications. Unlike coronary artery and peripheral vascular interventions, where symptomatic relief can be experienced after revascularization of a single vessel, clinical improvement following BPA is typically observed after revascularization of multiple diseased segments and regions. Furthermore, overly aggressive dilation of individual lesions increases the risk of pulmonary vascular injury and can be counterproductive to the overall treatment strategy.

Unfractionated heparin is routinely used for systemic anticoagulation in BPA due to the risk of pulmonary vascular injury and the potential need to reverse anticoagulation using protamine sulfate. It is also for these reasons that a low activated clotting time range of 200 to 250 seconds is targeted during each BPA procedure.

Soft,atraumatic 0.014-inch workhorse guidewires with spring-coil tips (rather than 0.035-inch wires or stiffened/jacketed specialty wires) are used for BPA. Nearly all of our BPA procedures are performed using the Hi-Torque Balanced Middle Weight (Abbott Vascular, Abbott Park, IL, USA) or Runthrough NS Extra Floppy (Terumo Corporation, Tokyo, Japan) guidewire. Even when treating occluded vessels, use of atraumatic wires in conjunction with balloon catheter support is preferred over initial wire escalation or use of stiffer wires. Early experiences with polymer-jacketed guidewires also demonstrated increased risk of vascular injury and pulmonary hemorrhage.

Initial balloon angioplasty is performed using small-diameter, compliant balloons to help determine vessel size and lesion response before utilizing larger diameter balloons. The majority of distal pulmonary vascular lesions can be initially treated using 2.0-mm diameter balloons. Balloon angioplasty of proximal pulmonary artery segments is performed across multiple sequential inflations and step-wise utilization of larger diameter noncompliant balloons typically ranging between 2.5 and 4.0 mm, and rarely up to 5.0 mm (Figure 2). Use of oversized balloons risks distortion of the pulmonary artery architecture and vessel perforation.

Special techniques are considered when target lesion recoil is observed despite serial balloon inflations and appropriate balloon sizing. First, serial prolonged balloon inflations up to 3 minutes in duration are attempted. Next, lesion modification using specialty devices such as the Chocolate (Teleflex Inc., Wayne, PA) and AngioSculpt (Phillips HealthCare, Best, the Netherlands) balloon catheters can be attempted with prolonged balloon inflation. More aggressive cutting balloon angioplasty or mechanical atherectomy increases risk of vessel injury and should be avoided. While long-term post-BPA pulmonary artery patency data are limited, restenosis is considered uncommon and stenting to prevent restenosis after BPA is not recommended especially due to significant pulmonary vascular mobility during the respiratory cycle. Deployment of covered stents for catastrophic vessel rupture is technically feasible and previously described.

Additional strategies, in addition to the aforementioned techniques, are employed to optimize BPA safety and patient outcomes. First, more aggressive BPA techniques are avoided during initial treatment sessions (especially in the presence of high-grade obstructions, total occlusions, or elevated baseline mean pulmonary artery pressure >35 mmHg) in order to minimize the risk of pulmonary vascular injury and hemoptysis. Second, BPA treatment is limited to 1 to 2 lobes of a single lung (3 to 5 segments) per individual treatment session to limit contrast and radiation exposure and attendant risks, and mitigate the potential extent of pulmonary vascular injury. Third, the safe approach for revascularizing occluded segments is to restore distal blood flow, improve hemodynamics, and provide a safe conduit and context for future repeat intervention, rather than achieve optimal angiographic results immediately.

Functional Assessment

Intravascular functional assessment may be warranted to evaluate pulmonary arteries that appear to be normal by selective pulmonary angiography but are associated with lung hypoperfusion by noninvasive lung perfusion imaging. In such cases, measuring ratio of distal-to-proximal pulmonary artery pressure (Pd/Pa) may be helpful to identify the presence of obstructive pulmonary artery disease. Furthermore, atraumatic guidewires will typically encounter resistance and require manipulation and/or balloon catheter support to traverse target vessels with underappreciated disease. Distal pressure measurement using a microcatheter-based manometer (Navvus MicroCatheter, Acist Medical Systems, Eden Prairie, MN, USA) can reveal pressure reduction during diastole alone, the entire cardiac cycle, or complete pressure dampening with increasingly severe disease. Additional investigation is needed to better understand these invasive pressure waveforms, fluctuations during the respiratory cycle, and the optimal cutoff defining severe pulmonary artery obstructive disease. Despite the lack of a standardized approach to guide BPA using functional measurements, our strategy has been to treat vessels having Pd/Pa <0.75 with additional balloon dilation (larger balloons, higher pressures, or scoring balloons/guidewires) and to accept any Pd/Pa improvement as sufficient to conclude immediate treatment within the target vessel. During follow-up functional assessments, depressed pressure ratios are improved either due to thrombus resolution or vascular remodeling following pulmonary artery revascularization. Intermittent noninvasive lung perfusion scans between BPA treatment...
sessions also help evaluate perfusion within treated segments and guide repeat intervention for areas of persistent hypoperfusion.

**BPA Complications**

**Early BPA Complications**

The earliest described BPA in 1986 was associated with postprocedural cough, hemoptysis, and radiographic pulmonary edema. These findings were attributed to reperfusion pulmonary edema (RPE) occurring in the regions of BPA treatment. A subsequent series of 18 CTEPH patients who underwent 47 BPA procedures described the development of RPE in 11 of 18 patients (61% of total patients), with 3 needing mechanical ventilatory support (17% of total patients), and one dying from right ventricular failure 7 days after BPA (6% of total patients). Pulmonary artery perforation from a stiff guidewire (2% of procedures) and 3 femoral artery pseudoaneurysms (6% of total patients). Pulmonary artery perforation from a stiff guidewire (2% of procedures) and 3 femoral artery pseudoaneurysms (6% of total patients). 22 Pulmonary artery perforation from a stiff guidewire (2% of procedures) and 3 femoral artery pseudoaneurysms (6% of total patients).

**Evolution of BPA and Contemporary BPA Complications**

Updated reports of BPA for CTEPH from multiple Japanese centers around 2012 described the use of using smaller diameter angioplasty balloons, thinner 0.014-inch guidewires, and intravascular imaging during BPA procedures. While the incidences of reported RPE (60%-68%), hemoptysis (50%), and wire perforation (3%) were similar to those reported over a decade earlier, there was interval reduction in major complications as observed by lower rates of positive pressure ventilation (7%), mechanical ventilation (3%-6%), percutaneous cardiopulmonary support (3%), and 12-month mortality (0%-3%).

Contemporary BPA centers worldwide have adopted or continued the use of thin flexible guidewires, small diameter angioplasty balloons, and staged BPA treatment sessions leading to improved patient outcomes. A series from Norway (20 patients), described 7 instances of RPE (10% of procedures) and 2 deaths (10% of patients; once from right ventricular failure, one from pulmonary embolism) after BPA. From Germany (56 patients, 266 procedures), 25 procedure-related complications were observed (32% of patients, 9.4% of procedures), mostly due to pulmonary vascular injury (arterial dissection without bleeding 0.8%, arterial bleeding without hemoptysis 1.1%, and hemoptysis 5.6%). The latest analysis of the audited University of California, San Diego BPA Registry (95 patients, 402 procedures) revealed low incidences of asymptomatic pulmonary vascular injury (1.5% of procedures) and uncomplicated hemoptysis (8% of procedures). RPE, mechanical ventilation, or death did not occur. Outcomes from the largest reported BPA cohort combining patients from multiple BPA centers across Japan (308 patients, 1408 procedures), also reported fewer overall procedural complications, including hemoptysis (14.0%), angiographically apparent pulmonary artery perforation (2.9%), dissection (0.4%), and vessel rupture (0.1%) compared to initial reports from 2012. Moreover, severe complications, including mechanical ventilation (5.5%), extracorporeal membrane oxygenation (2.9%), coil embolization (1.6%), and covered stenting (1.0%), were also infrequent. Twelve-month mortality after initial BPA therapy was 3.2%.

The most common intraprocedural complication of BPA is pulmonary artery injury (9.4%-17.8%) sometimes leading to hemoptysis (5.6%-14.0%), overt pulmonary artery dissection (0.4%), or rupture (0.1%). Pulmonary artery injury can result from distal wire perforation, balloon over-dilation, and high-pressure contrast injection. Acute management of pulmonary artery injury aims to 1) treat vascular injury, 2) support respiratory function, and 3) avoid cardiopulmonary collapse (Table 2).

Pulmonary artery injury is considered to be associated with iatrogenic bleeding into the lung parenchyma, and is observed in the context of pulmonary vascular injury (1.5% of procedures) and uncomplicated hemoptysis (8% of procedures). RPE, mechanical ventilation, or death did not occur. Outcomes from the largest reported BPA cohort combining patients from multiple BPA centers across Japan (308 patients, 1408 procedures), also reported fewer overall procedural complications, including hemoptysis (14.0%), angiographically apparent pulmonary artery perforation (2.9%), dissection (0.4%), and vessel rupture (0.1%) compared to initial reports from 2012. Moreover, severe complications, including mechanical ventilation (5.5%), extracorporeal membrane oxygenation (2.9%), coil embolization (1.6%), and covered stenting (1.0%), were also infrequent. Twelve-month mortality after initial BPA therapy was 3.2%.

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patient coughing, hemoptysis, and contrast extravasation by angiography. Vessel injury is initially managed by immediately performing balloon tamponade and identifying the cause of injury. When distal wire perforation occurs, the wire is carefully repositioned back into a safe position. When balloon over-dilation occurs, vessel re-injury is avoided during balloon tamponade via low pressure inflations and balloon repositioning within an optimal vessel segment. Administration of additional systemic anticoagulation is also halted during initial management. Repeat prolonged balloon tamponade and reversal of systemic anticoagulation are also employed for persistent bleeding.14 This is why systemic anticoagulation using unfractionated heparin and a low activated clotting time goal of 200-250 seconds is targeted during every BPA procedure. Bailout treatments using transcatheater coil embolization,15,16,25 covered stent implantation,17,26 and/or injection of gelatin or adipose into the target vessel have been previously described for severe persistent pulmonary hemorrhage.2,9 Emergent surgery with chest tube insertion, hematoma evacuation, and/or lobectomy may be necessary to definitively manage bleeding in extreme situations.

Impaired respiratory function due to BPA complications is managed expectantly, with initial administration of supplemental oxygen by nasal cannula and monitoring for hemoptysis. Face mask oxygenation and oropharyngeal suctioning may also be useful for patients with preferential mouth breathing. For suboptimal blood oxygenation despite these initial measures, administration of high concentration oxygen by face mask or high-flow nasal cannula can be used. Patients with a greater degree of vascular injury and lung sequelae may need additional noninvasive positive airway pressure support.17,18 The use of diuretic or inhaled nitric oxide therapy, previously described for the treatment of reperfusion pulmonary edema,22,23 is not clearly established for improving oxygenation due to pulmonary hemorrhage. Infrequently, patients with severe pulmonary vascular injury and respiratory complications during BPA require endotracheal intubation and mechanical ventilation to maintain adequate respiratory function and facilitate the ongoing management of concurrent bleeding and/or cardiopulmonary collapse.

Patients with CTEPH undergoing BPA commonly have baseline compromised pulmonary reserve due to ventilation-perfusion mismatch as well as compromised cardiac reserve due to longstanding pulmonary hypertension and right ventricular dysfunction. Severe pulmonary vascular injury and pulmonary hemorrhage during BPA can lead to further compromise of respiratory function, severe hypoxemia, further depression of cardiac function, and initiate a vicious cycle of cardiopulmonary and multigorgan failure. Management of severe pulmonary vascular injury should sufficiently support both respiratory and circulatory function, and immediate control of bleeding should be achieved as soon as possible. When noninvasive positive pressure ventilation does not provide sufficient oxygenation or pneumatic suppression of pulmonary hemorrhage, then mechanical intubation should be quickly performed.20 Significant bleeding into a unilateral airway and massive hemoptysis should be managed by lateral decubitus positioning toward the impaired lung and selective intubation of the contralateral lung. Significant bleeding into the pleural space and occurrence of tension hemothorax may require emergent chest tube insertion, fluid resuscitation, and blood transfusion. Rescue extracorporeal membrane oxygenation support for ongoing respiratory and circulatory failure may be needed to stabilize patients and provide a bridge for emerging surgical and nonsurgical interventions and cardiopulmonary recovery.

**BPA Outcomes**

BPA therapy is associated with improvements in cardiopulmonary hemodynamics, right ventricular function, ventilation efficiency, functional classification, 6MWD, and high follow-up survival.31,32,34-36 Observations of 308 patients from the Japanese multicenter BPA registry included clinical improvement of median WHO functional class from 3 to 2, 6MWD from 318.1 ± 122.1 to 429.7 ± 108.5 meters, and supplemental oxygen rate from 2.5 ± 2.0 to 0.5 ± 0.8 L/min (all p < 0.001). Hemodynamic improvements in heart rate (74.9 ± 13.6 to 67.3 ± 11.0 beats/min), mean pulmonary artery pressure (43.2 ± 11.0 to 22.5 ± 5.4 mmHg), pulmonary vascular resistance (PVR) (from 853.7 ± 450.7 to 288.1 ± 194.5 dyne·cm⁻²/m²), cardiac index (from 2.6 ± 0.8 to 2.8 ± 0.6 L/min/m²), and arterial oxygen saturation (93.3 ± 4.5 to 94.0 ± 5.2%) were also observed after BPA therapy (all p < 0.001). Survival after BPA, based on the multicenter Japanese registry, was 96.8% at 1 and 2 years, and 94.5% at 3 years for all subjects. Survival for the subset of 249 subjects considered to have completed BPA therapy was 98.9% at 1, 2, and 3 years.19

Additional clinical and hemodynamic observations of 154 eligible patients from a French single-center BPA registry included similar improvements of New York Heart Association functional class, 6MWD (from 396 ± 120 to 441 ± 104 meters), mean pulmonary artery pressure (from 43.9 ± 9.5 to 31.6 ± 9.0 mmHg), cardiac index (from 2.68 ± 0.60 to 3.07 ± 0.75 L/min/m²), and PVR (from 604 ± 226 to 329 ± 177 dyne·cm⁻²/m²) after BPA therapy (all p < 0.001).20 Survival of the 184 overall French registry participants at 1 and 3 years after BPA was 97.3% and 95.1%, respectively.

Results of the Riociguat vs. Balloon Pulmonary Angioplasty in Non-Operable Chronic Thromboembolic Pulmonary Hypertension (RACE) randomized clinical trial are congruent with these real-world registry findings.31,32 First, subjects in the RACE trial BPA treatment arm experienced a 60.1% reduction of mean PVR by 26 weeks after randomization, similar to the 58% and 42% PVR reduction observed at unspecified post-BPA timepoints in the Japanese and French BPA registries, respectively.20,36 Second, treatment-related severe adverse events in the RACE trial occurred in 14% of BPA sessions and 42% of BPA patients, most commonly related to hemoptysis (15% of patients), compared to 9% of patients treated with riociguat. BPA-related hemoptysis was observed in 14.0% and 11.2% of procedures from the Japanese and French BPA registries, respectively. BPA therapy vs. riociguat in the RACE trial was associated with greater pulmonary artery pressure reduction (18.7 mmHg vs. 5.1 mmHg), lower post-treatment PVR from baseline (39.9% vs. 66.7%), lower post-treatment N-terminal pro-brain natriuretic peptide from baseline (21.1% vs. 57.4%), and more frequent improvement of WHO functional classification (88% vs. 49%) at week 26 of treatment (all p < 0.0001).

Hemodynamic improvements, such as mean pulmonary artery pressure and PVR, are proportional to the number of vessels treated during BPA therapy7,28 and may take weeks after each procedure for the effects to be observed.31,33 Improved hemodynamics after BPA is also associated with reduced level of circulating high-sensitivity troponin and subclinical myocardial injury,34 positive RV remodeling, and improved systolic function. Improved RV function after BPA has been demonstrated by speckle tracking and three-dimensional echocardiographic techniques and cardiac magnetic resonance imaging.27,35,36 Secondary renal function improvement after BPA therapy and improved hemodynamics has also been observed in CTEPH patients with baseline renal dysfunction.7,28

**Conclusions**

BPA, in conjunction with medical therapy, has an important and expanding role in treating CTEPH patients who are not candidates for PTE surgery. The worldwide adoption and continuous refinement of BPA since its inception in 1986 has led to advancements in the equipment used, technical approach, and complication management for BPA procedures. Contemporary BPA outcomes include various clinical and hemodynamic improvements and a high survival rate for patients after completion of therapy.

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