CLINICAL EVIDENCE SUMMARY

Balloon Occlusion Transcatheter Arterial Embolization

Embolization through balloon occlusion microcatheters is a new technique that appears to improve liver tumor response and survival as well as safety through avoidance of non-target embolization in prostatic artery embolization (PAE). We postulate that this new technique is an advancement in embolization therapy and that routine use should yield improved patient outcomes.

SUMMARY

There is a growing body of literature from both animal and clinical studies supporting the use of balloon occlusion microcatheters in liver tumor embolization and prostatic artery embolization. Additional balloon occlusion studies are underway that will expand clinical understanding not only in liver and prostate arterial embolization, but also will explore new treatment areas including, but not limited to, uterine fibroid embolization, and hemorrhoid embolization.

Balloon occlusion of a supply artery produces hemodynamic alterations to blood flow that permits increased therapeutic agent delivery into targeted tumors and prostates while providing both antegrade and retrograde non-target embolization protection (1,2,3). This technique has been used to successfully improve patient outcomes as highlighted in the following results further described in this paper:

- 2.4 times the number of microspheres delivered to the distal embolization target when the balloon was inflated compared to when the balloon was deflated (similar to conventional end-hole microcatheter delivery) (2).
- Two-fold to seven-fold improvement in lipiodol density in tumors where balloon occlusion was used for segmental delivery as opposed to conventional end-hole delivery (5,6).
- 53% improvement in 5-year survival when using a balloon occlusion microcatheter as opposed to conventional end-hole delivery (8).
- 41% improvement in complete tumor response when using a balloon occlusion microcatheter as opposed to conventional end-hole delivery (10).
- Balloon occlusion prostatic artery embolization is technically feasible and can be performed safely with no adverse events recorded (18,19). No coils or gel foam were used to protect prostate anastomosis from non-target embolization. 16-point decrease in International Prostate Symptom Score at 22-week follow-up (19).

PRESSURE-DIRECTED EMBOLIZATION

Balloon occlusion transcatheter arterial embolization is based on a well-established physical property of fluid dynamics, whereby liquids always flow from high pressure to low pressure environments. Balloon occlusion of a supply artery produces pressure mediated hemodynamic changes that increase therapeutic agent delivery into targeted tumors, prostates or fibroids with antegrade and retrograde non-target embolization protection (1,2,3). This technique is called pressure-directed embolization. There are two methods to achieve pressure-directed embolization: selective and nonselective delivery.

With *selective delivery*, the balloon occlusion microcatheter is advanced to a distal location where the embolization target is isolated. When the balloon is inflated and the supply artery is occluded, embolic agents are injected into this target area past the point of stasis. As embolization progresses, pressure increases in the target area beyond systemic circulation. This causes a greater degree of microvascular embolic penetration into the tumor, prostate or other anatomical target. The inflated balloon prevents retrograde flow (reflux) from traveling to non-target locations. Embolic agents are injected until observation of embolic reflux around the balloon or the balloon “pushing back” in the vessel or observation of contrast in the portal vein (1,2,3).

With *nonselective delivery*, the balloon occlusion microcatheter is advanced to a proximal location where branch arteries are evident between the microcatheter’s tip and embolization target. When the balloon is inflated and the supply artery is occluded, an area is created distal to the microcatheter tip that is at a lower pressure than that of the systemic circulation. This causes the blood flow to slow down and redistribute such that flow from adjacent arterial networks is redirected into this lower-pressure vascular compartment and ultimately into the lowest pressure tumor, prostate, or fibroid.

TABLE 1: Summary of Publications Comparing Tumor Response Rates of Balloon-Occlusion TACE to Conventional End-Hole TACE for Treatment of HCC

Study	Total No. of Patients	Balloon Occlusion TACE					Conventional End-hole Microcatheter TACE				
		No. of Patients	TE4 (%)	TE3 (%)	TE2 (%)	TE1 (%)	No. of Patients	TE4 (%)	TE3 (%)	TE2 (%)	TE1 (%)
Arai et al. 2015 (7)	97	49	55.1	38.8	4.1	2.0	48	39.6	33.3	25.0	2.1
Ogawa et al. 2016 (8)	61	33	49.2	50.8 (TE3+TE2+TE1)			28	27.0	73.0 (TE3+TE2+TE1)		
Irie et al. 2016 (9)	77	28	89	11	0	0	49	65	20	6	8
Ogenstad 2017 (10) Meta-analysis of clinical studies	Compared TE4 (Disappearance or 100% necrosis of all treated tumors) Showed balloon occlusion TACE provides a 41% TE4 improvement (95% confidence, p-value = 0.004)										

Note—TE4-TE1 = tumor response rates (treatment effect) proposed by the Liver Cancer Study Group of Japan, RECICL criteria 2009 version.
TE4: Disappearance or 100% necrosis of all treated tumors
TE3: ≥50% reduction in tumor size, >50% tumor necrosis, or both
TE2: A response not qualifying for classifications TE1, TE3 or TE 4
TE1: ≥25% increase in tumor size regardless of necrotic effect

Embolic agents are injected slowly to maintain low pressure. The embolization endpoint is achieved with observation of contrast stasis in the distal arteries (1,2,3).

MECHANISM OF ACTION STUDIES

In 1997, Rose et al. published on the use of a balloon occlusion catheter during splenic artery embolization. Occlusion of the main splenic artery resulted in flow reversal in non-target arteries and protection of adjacent organs in the downstream splenic artery. When the balloon was deflated, gentle hand injection of contrast material resulted in opacification of non-splenic arteries. When the balloon was inflated, a 41 mmHg reduction in blood pressure was measured, and gentle hand injection of contrast material resulted in opacification of only the splenic arteries and no opacification of non-splenic arteries (1).

In 2016, in an NSF funded animal study (n=5 pigs), Rose et al., confirmed preferential flow redistribution resulting from balloon occlusion. The study showed that 2.4 times the number of microspheres were delivered to the distal embolization target when the balloon was inflated compared to delivery when the balloon was deflated (similar to conventional end-hole microcatheter delivery). Inflation of the balloon microcatheter in the segmental hepatic artery resulted in a consistent and significant decrease in blood pressure (mean: 30 mmHg; range 23-43 mmHg; $p<0.05$) in the downstream vascular compartment (2).

In 2019, Rose et al., describes the hemodynamic alterations to blood flow caused by the deployment of balloon occlusion microcatheters and the resulting changes to embolic distribution. Compared with embolic agents delivered through a conventional end-hole microcatheter, embolic agents delivered via a balloon occlusion microcatheter have substantially different distributions due to the altered blood flow patterns. Under conditions of reduced downstream compartmental pressures, embolic agents are largely prevented from flowing to non-target structures and are preferentially delivered into the targeted tumor. The distribution of embolic agents into tumors that extend beyond the downstream targeted compartment (i.e., watershed tumors that have a supply artery that originates from adjacent liver segments) may be less predictable and may depend on whether embolization is performed under conditions of reduced or increased pressure. The key to optimizing the outcome is understanding and control of the hemodynamic forces at play (3).

LIVER STUDIES

There is a growing body of evidence that suggests liver tumor embolization through a balloon occlusion microcatheter improves tumor response and survival.

Improvement in Lipiodol filling and relationship with tumor response: In 1994, Murakimi, in a 36-patient study, demonstrated that incomplete lipiodol filling resulted in 100% tumor recurrence as opposed to 13% recurrence with complete lipiodol filling (4). This showed a strong correlation between the amount of lipiodol in a tumor and tumor response. Irie et al showed a seven-fold improvement in lipiodol density in tumors where balloon occlusion was used for segmental delivery as opposed to conventional end-hole delivery (5). Maruyama et al. reproduced the benefit of balloon embolization in a 100-patient study where a two-fold improvement was found in lipiodol density when segmental balloon embolization was used opposed to conventional end-hole delivery (6).

Use of a balloon occlusion microcatheter produces improved tumor response relative to use of a conventional end-hole microcatheter: In a series of HCC conventional TACE studies completed between 2015 and 2016, use of balloon occlusion microcatheters was compared with the use of conventional end-hole microcatheters. Microcatheter tip placement in these studies was segmental or subsegmental (Table 1). In 2015, Arai et al., in a 97-patient study, showed that tumor response was markedly improved when balloon occlusion embolization was used (7). Most striking, TE4 (complete tumor response) was improved by 39%. Ogawa et al., in a 61-patient study, showed an 81% improvement in complete response when balloon occlusion embolization was used (8). Irie et al. completed an outcome study that included both tumor response and 1, 3 & 5-year survival with complete response improving by 37% and TE's 1&2 (stable disease or progressive disease) reduced to 0%. Most notably, 3-year survival was improved by 63% and 5-year survival improved by 53% (9). A meta-analysis (10) was completed on tumor response data from these three aforementioned studies (7,8,9) using a random effects model. The combined data shows a 41% improvement in complete tumor response with a 95% confidence and a p-value of 0.004 (highly significant) when using a balloon occlusion microcatheter.

Complete response resulting from an initial TACE procedure has the longest overall survival: In 2016, Kim et al. conducted a 314-patient study demonstrating that long term survival was directly related to achieving a complete tumor response early in the course of embolization therapy. Patients with a complete response as initial response (first TACE) had the longest survival rate. Patients that received a complete response during the second, third or fourth TACE procedure had the second longest survival rate and patients who only received partial tumor response had the shortest survival rate (Table 2) (11). This study is of interest since balloon occlusion embolization produces an improved tumor response early in embolization therapy (7,8,9).

TABLE 2: Survival Associated with Early TACE Response

Response	Survival
Complete response at 1st TACE with complete disappearance of viable lesions	5.8 years (70.2 months)
Complete response at 2nd, 3rd or 4th TACE	3.4 years (40.6 months)
Only partial response with ≥ 30% decrease from baseline	1.9 years (23.0 months)
Persistent non-response	1.1 years (13.3 months)

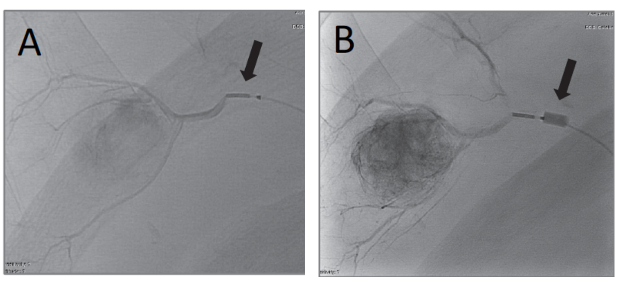
Recent single center experience at Mount Sinai, New York, showed 100% technical success rate and favorable safety profile and tumor response for HCC treatment: In 2018, Goldman et al. conducted a 26-patient study utilizing balloon occlusion microcatheters with both conventional TACE and drug eluting beads (DEB) TACE. Procedural safety was favorable with no intra-procedural complications in 100% of patients. No angiographic abnormalities (e.g. no vessel damage) were observed in the patients that underwent angiography following balloon occlusion TACE at a mean follow-up time of 3 months. 60% of treated tumors demonstrated complete response and no regional recurrence in 100% of patients evaluated (12). Similarly, in 2018, Lucatelli et al. conducted 22-patient study utilizing balloon occlusion microcatheters with DEB-TACE. At a mean follow-up time of 3-6 months, 52.9% of treated tumors demonstrated a complete response (13). To provide context, in 2015 Vesselle et al. conducted a 172-patient study utilizing conventional end-hole microcatheters and DEB-TACE. After a one to two-month follow-up period, complete response was observed in only 36% of treated tumors (14). Further, in 2017 Jeong et al. conducted a 287-patient study utilizing conventional end-hole microcatheters with conventional TACE. After a one-month follow-up period, complete response was observed in only 28.2% of treated tumors (15).

Case study—Balloon occlusion microcatheter use with microwave ablation to treat HCC with complete response outcome: In 2018, Fischman et al. evaluated DSA (Figure 1) and CT imaging and demonstrated increased tumor enhancement with decreased surrounding parenchymal enhancement when the balloon was inflated versus when the balloon was deflated (similar to conventional end-hole microcatheter delivery).

Given the successful case outcome and no tumor recurrence at 1-year follow-up, Fischman concludes that balloon occlusion TACE may be advantageous in HCC treatment and can be used as a method to increase complete response when used with microwave ablation and as a method of defining ablation margins (14).

Case study—Balloon-assisted TACE segmentectomy: an alternative strategy in the treatment of hypovascular oligometastatic liver metastases: In 2018, Stein et al. describes the use of a balloon occlusion microcatheter to treat a patient with two hypovascular oligometastatic liver tumors of pancreatic adenocarcinoma origin that would have been difficult to successfully ablate given their poorly defined margins. Segmental placement of the balloon occlusion microcatheter was achieved and liver segmentectomy was performed on both segments 4A and 2. 16-months after the balloon occlusion TACE segmentectomy procedure there were no evidence of local recurrence of pancreatic adenocarcinoma metastases (15).

FIGURE 1: DSA demonstrating increased tumor enhancement with balloon occlusion microcatheter. Balloon inflated (image B at black arrow) versus deflated (image A at black arrow).



Case study—Pressure Directed Balloon-Assisted TACE for unresectable HCC: In 2018, Stein et al. describes the use of a balloon occlusion microcatheter to treat a 10.5 cm HCC tumor in liver segment 7. The pressure directed reversal of flow away from non-target vessels was visualized and post procedural imaging at 1 month demonstrated diminished enhancement of the treatment area. Stein concludes that the use of a balloon occlusion microcatheter can be a useful tool to navigate complex anatomy and preserve vital structures during TACE (16).

Balloon occlusion microcatheter used to optimize transarterial therapies for the treatment of hepatic malignancy: In 2018, Kouri describes the use of a balloon occlusion microcatheter as a strategy for overcoming non-target cystic artery embolization and to enable single dose infusion in radioembolization. Two possible approaches were defined. One approach is to place the balloon occlusion microcatheter at the cystic artery origin for protection. Another approach is to place a balloon occlusion microcatheter into cystic artery with a second microcatheter positioned proximally to deliver the embolic agent. The balloon on the distally placed microcatheter can be inflated during the embolization for protection, but then deflated and removed at the end of the case (17).

PROSTATE STUDIES

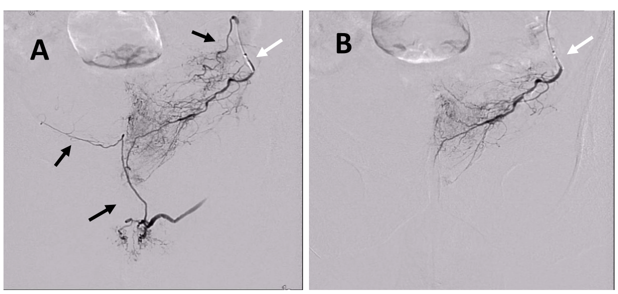
There is also clinical evidence that suggests prostatic artery embolization (PAE) through a balloon occlusion microcatheter improves procedure safety through avoidance of non-target embolization.

Use of balloon *occlusion microcatheter to avoid non-target flow during PAE procedures:* In 2015, Abele et al. evaluated prostate perfusion using Tc-99m MAA after selective prostate artery catheterization with a conventional end-hole microcatheter. The study showed 12 out of 14 patients had non-target flow and 8 out of 14 had non-target flow to more than one location. This clearly demonstrates that non-target flow is common in PAEs when using end-hole microcatheters, even when infusion is from a selective location (18). In 2017, Keasler et al. assessed prostatic digital subtraction angiography through a balloon occlusion microcatheter in a 12-patient study and found inflation of the balloon not only prevents reflux but also results in altered blood flow within and around the prostate. The angiograms from the study demonstrated that the inflated balloon prevented reflux of contrast material into small vesicular branches arising proximally from the prostatic artery. Extraprostatic arterial anastomosis arising distal to the prostate that were visible on angiography with the balloon deflated, were not visible after balloon inflation (19). In 2018, Isaacson et al. conducted a 12-patient study to assess the feasibility of using a balloon occlusion microcatheter for PAE. The study found balloon occlusion PAE technically feasible and able to be performed safely with no adverse events recorded. In the study, no coils or gel foam were used to protect the anastomosis from non-target embolization. On balloon-occlusion angiography, 5 of 6 penile anastomoses (83%) and 5 of 6 rectal anastomoses (83%) were no longer evident. Catheterization was successful in all prostatic arteries with the use of a balloon occlusion microcatheter. At 22-week follow-up patient symptom score (IPSS) improved from severe (score of 23) to mild (score of 7) and quality of life score improved from unhappy (score of 5) to pleased (score of 1) (20).

Case study—Balloon occlusion microcatheter use to provide an option for distal protection in prostatic artery embolization: In 2018, Ayyagari et al. describes a case where a balloon occlusion microcatheter can be used to provide distal protection from non-target embolization in addition to its traditional use in preventing non-target embolization through pressure direction and reflux avoidance. The balloon occlusion microcatheter was deployed distally to protect the downstream obturator artery territory. The prostatic artery was then treated by proximal injection of 100-300 µm microsphere particles through the hemostatic valve where the particles flowed through the annular space between the 5-F diagnostic catheter and microcatheter (21).

Clinical conference presentation—Balloon Occlusion Microcatheter for PAE: In 2018, Bilhim presented single center experience (Saint Louis Hospital, Lisbon, Portugal) with balloon occlusion at the STREAM PAE conference in Washington D.C. Bilhim presented a number of PAE cases at STREAM describing both antegrade and retrograde non-target embolization protection (Figure 2) (22).

FIGURE 2: PAE case presented at the STREAM PAE conference in Washington D.C. Balloon deflated (image A at white arrow) versus inflated (image B at white arrow). Balloon inflation results in nontarget embolization protection through distal flow redistribution of two anastomoses and proximal reflex elimination (image A, black arrows).



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