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# Feasibility of Combination Intra-arterial Yttrium-90 and Irinotecan Microspheres in the VX2 Rabbit Model

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## Abstract

**PURPOSE:** To evaluate the combination of $^{90}$Y radioembolization (Y90) and drug-eluting bead irinotecan (DEBIRI) microspheres in the VX2 rabbit model.

**MATERIALS & METHODS:** An initial dose finding study was performed in 6 White New Zealand rabbits to identify a therapeutic but subcurative dose of Y90. 29 rabbits were used in four groups: Y90 treatment (n=8), DEBIRI treatment (n=6), Y90+DEBIRI treatment (n=7) and an untreated control group (n=8). Hepatic toxicity was evaluated at baseline, 24hrs, 72hrs, 1 week, and 2 weeks. MRI tumor volume (TV) and enhancing tumor volume (ETV) were assessed baseline and two weeks. Tumor area and necrosis were evaluated on H&E for pathology.



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**Conflict of Interest:** RAO and ACL are founders and owners of IO-RAD and received grant funding from BTG for this study. SBW is a consultant for IO-RAD and Guerbet, and receives research support from Siemens and Guerbet. RJL and RS served as scientific advisors to BTG. RJL is a consultant for ABK. MRD is an employee of BTG. None of the other authors have identified any conflict of interest.

**RESULTS:** Infused activities of 2.27–2.55mCi (corresponding to 55.1–72.7 Gy) were selected based on the initial dose finding study. Infusion of DEBIRI after Y90 was technically feasible in all cases (7/7). Overall, 21/29 animals survived to 2 weeks, the remaining animals had extrahepatic disease on necropsy. Liver transaminases were elevated with Y90, DEBIRI, and Y90+DEBIRI compared to control at 24hrs, 72hrs, and 1 week post-treatment and returned to baseline by 2 weeks. By TV, Y90+DEBIRI was the only treatment to show statistically significant reduction at two weeks compared to the Control group (p=0.012). The change in tumor volume (week 2 – baseline) for both Y90+DEBIRI versus Control (p=0.002) and Y90 versus Control (p=0.014) were significantly decreased. There were no statistically significant differences among groups on pathology.

**CONCLUSION:** Intra-arterial Y90+DEBIRI was safe and demonstrated enhanced antitumor activity in rabbit VX2 tumors. This combined approach warrants further investigation.

## Summary Statement:

Irinotecan drug eluting microsphere administration immediately after $^{90}$Y radioembolization is feasible and combination treatment improved antitumor activity in the VX2 rabbit model.

### Keywords

radioembolization; chemoembolization; magnetic resonance imaging; yttrium-90; irinotecan

## INTRODUCTION

Radioembolization with yttrium-90 microspheres (Y90) is a salvage therapy for chemotherapy resistant/refractory liver-predominant metastatic colorectal cancer (mCRC) and is now included in the National Comprehensive Cancer Network guidelines (1). This locoregional therapy has been broadly applied in the setting of unresectable hepatic malignancies including hepatocellular carcinoma (2), intrahepatic cholangiocarcinoma (3), breast cancer liver metastases (4,5), and other liver-dominant metastases (6–8). A micro-embolic therapy, Y90 with glass microspheres results in minimal reductions to antegrade blood flow and the goal of therapy is delivery of radiation rather than the induction of tumor ischemia (9). In theory, preserved antegrade arterial blood flow to hepatic tumors could allow immediate delivery of additional intra-arterial therapies like chemotherapy and/or radiosensitizing agents at the time of treatment to enhance or synergize radioembolization therapies. Irinotecan is a camptothecin derivative and is now included early in the treatment algorithm for mCRC and its mechanism of action depends on functional hepatic parenchyma for conversion to its active form (SN-38) with antitumor activity via inhibition of topoisomerase I with clinical interest in combination with radiation therapy for non-small cell lung cancer treatment (1,10). Recent clinical trials have investigated the safety of intra-arterial drug-eluting beads loaded with irinotecan chemoembolization (DEBIRI) in mCRC (11–15). Both Y90 and DEBIRI have been used for surgical downstaging and neoadjuvant therapy in mCRC in small retrospective series (16–18). While these minimally invasive therapies are clinically applied in the salvage setting, we sought to explore whether the combination of Y90 and DEBIRI would result in improved antitumor activity. The purpose of this pilot study was to test the feasibility of delivering combination intra-arterial therapy

with Y90 immediately followed by DEBIRI in the VX2 rabbit model and to evaluate the safety, and antitumor outcomes of this combination in comparison to either therapy alone. We hypothesized that the combination could be safely delivered and result in improved antitumor effect.

## MATERIALS & METHODS

### VX2 Animal Model and US-guided Tumor Implantation

Our institution's animal care and use committee approved this study, and all procedures were performed under institutional guidelines. The use of glass $^{90}$Y microspheres for research was approved and overseen by the Radiation Safety Officers of the university and associated hospital system. A total of 33 White New Zealand rabbits weighing 3–4 kg were implanted in the liver for this study (Covance Laboratories, Greenfield, IN). The propagation of VX2 cells and implantation technique have been previously reported (19). A dose finding study was performed to identify a subcurative yet therapeutic dose of Y90 in rabbit VX2 tumors. In the dose finding study, five tumors were implanted in the left and right lobe (3 in the left and two in the right) to simulate metastatic disease. Subsequently, tumor implantation was limited to three positions in the left hepatic lobe for all remaining rabbits. Of the 33 implanted rabbits, 8 were control rabbits, 8 Y90 rabbits treated with Dose A, 4 Y90 rabbits treated with Dose B, 6 DEBIRI rabbits, and 7 Y90+DEBIRI rabbits.

### MR Imaging Protocols

All MRI studies were performed at 7 Tesla using a 20-cm bore Bruker ClinScan magnet (Bruker Biospin MRI GmbH, Ettlingen, Germany) for confirmation of tumor growth 2–3 weeks after implantation. Enhancement was defined as increased signal relative to the normal hepatic parenchyma. Tumor volume (TV) was measured as the outer tumor margin on Gd-enhanced T1W images manually contoured using ImageJ Software Package (NIH). The non-enhancing tumor volume was measured and enhancing tumor volumes (ETV) was calculated as ETV = TV – NTV were measured for each lesion at baseline at 2-week follow-up interval. The change in TV at week 2 from baseline (ΔTV) was ΔTV = TV week 2 – TV week 0. Similarly, the change in ETV was ΔETV = ETV week 2 – ETV week 0. MRI sequence parameters appear in the Supplemental Materials & Methods.

### Laboratory Toxicity

Blood draws at baseline, 24hrs, 72hrs, 7-days, and 14-days post-treatment. Samples were preserved on ice and spun down to separate the serum for a panel including serum albumin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatine kinase (CK), and total serum bilirubin.

### $^{90}$Y Radioembolization and $^{90}$Y Dosing

Radioembolization was performed by infusing 20–30μm glass $^{90}$Y microspheres (TheraSphere®, BTG, London, UK) followed by 30–40cc of sterile 0.9% saline over 3–5 minutes, depending on native vessel flow rates. Dose vials calibrated at 1 GBq (9mg microspheres) were used in each animal and infused 8–9 days post-calibration, and all treatments occurred within 24hrs of baseline MRI. Following radioembolization, the

delivered dose was calculated according to the standard clinical paradigm (20). Infused volumes were calculated with manually drawn contours on MR images based on catheter tip positioning at the time of treatment. Administered activities are included in Table 1.

### DEBIRI Treatment and Dosing

Preloaded DEBIRI M1 beads containing irinotecan hydrochloride (50mg/cc irinotecan) loaded into LC Bead M1 (70–150μm diameter, BTG, London, UK) were used in this study and suspended by hydrating the DEBIRI bead volume (0.04cc) within 0.8cc total volume (1:20 ratio) of 1:1 saline/contrast mixture. This mixture was slowly infused by flushing the catheter with diluted contrast using 0.2cc aliquots of bead suspension (0.01cc bead volume) infused in each animal, while monitoring for changes to forward flow on DSA images. Two DEBIRI rabbits received four 0.2cc aliquots (2mg irinotecan in 0.8cc) volume. These rabbits did not survive. One DEBIRI rabbit received three 0.2cc aliquots and this resulted in sluggish antegrade flow. Therefore, remaining DEBIRI infusions were limited to two aliquots (0.02cc total bead volume) to reduce the bead volume and embolic load to the liver. Of the 10 additional animals treated with DEBIRI (3 rabbits for DEBIRI group, 7 rabbits for Y90+DEBIRI group), the infusion endpoint was administration of the total administered bead volume (1mg irinotecan in 0.4cc bead suspension) and was achieved in each case.

### Y90 + DEBIRI Group:

For animals in the combined treatment group, radioembolization was first performed and the catheter was then removed after infusion. Then the rabbit was catheterized again for the DEBIRI procedure (above). For DEBIRI infusion, the same catheter tip position was achieved as that for Y90 infusion in each case. Antegrade flow was confirmed prior to infusion of the DEBIRI microspheres and was present in all cases.

### Necropsy & Histopathology

After completion MRI at the study endpoint 2-weeks after treatment, all animals were euthanized and livers explanted. Hematoxylin & eosin (H&E) staining was performed and the slides digitized with optical magnification. Total tumor area (TA, viable and necrotic), viable tumor area (VA), and percentage of viable tumor area, for each lesion, were evaluated for each tumor. Digitized slides were made from 8–10 evenly spaced sections from each tumor (number of sections dependent upon the tumor size). Within each digitized slide, regions-of-interest (ROI) were drawn to encompass the outer tumor margin to calculate the total tumor area (TA). The necrotic portion of tumor was then contoured with ROI to calculate the necrotic area (NA). The viable tumor area (VA) was then calculated as VA=TA-NA and percentage of viable tumor area (VA% = VA x 100% / TV) for each tumor. Examples of MRI and histology tumor measurements are shown in Figure 1.

### Statistical Analyses

Statistical analyses for outcome comparisons between the different treatment groups were limited to those animals that reached the full two-week follow-up endpoint. The attrition was similar in each group with statistical analyses based upon data obtained from a total of 21 of 29 rabbits: 5 of 8 control rabbits, 6 of 8 Y90 rabbits, 4 of 6 DEBIRI rabbits, and 6 of 7

Y90+DEBIRI rabbits. Comparison plots and statements of statistical significance between groups are based upon the aggregate MRI or pathology data from tumors in these animals that reached the 2-week study endpoint. SPSS software package (version 15.0) was used for all statistical analyses. Data are reported as means ± standard deviation (SD) or medians with 95% confidence intervals (CI). Normal distributions were assumed for continuous outcome variables including labs, overall and viable tumor volume measurements on MRI, as well as measurements of the percentage of viable tumor volume (histology). Each of these measurements was compared between treatment groups using one-way analysis of variance (ANOVA) with Bonferroni post-hoc correction in cases where significant differences were detected for any set of outcome variables. All analyses were two-tailed and considered statistically significant at $P$ values less than 0.05.

## RESULTS

### VX2 Tumor Growth

Tumor growth was confirmed in all rabbits at a mean of 17.2 ± 1.1d. Multifocal implanted liver tumors demonstrated highly aggressive disease over follow up. Overall, 21 rabbits remained sufficiently healthy to be survived for the complete two-week post-treatment interval. Eight treated rabbits could not be survived for the complete two-week post-treatment interval. Of these, 3 were found deceased (prior to 2-week endpoint) and 5 had to be humanely euthanized due to marked health decline (lethargy, anorexia, and/or high resting respiratory rate). Innumerable lung, peritoneal, and spleen metastases were observed in each of these animals at necropsy.

### Dose Finding Study

Residual vial activities were 13–15% for **Group A (High Dose**, 55.1–72.7 Gy, n=2**)** and **B (Low Dose**, 6.1–8.1 Gy, n=4**)** rabbits. Independent of metric (whether whole tumor volume or enhancing tumor volume), nearly all tumors in Group B rabbits progressed (Figure 2). At Group A dosing, 38% (3/8) of the tumors had decreased tumor volume at 2 weeks versus 0% (0/11) of Group B tumors. The maximum observed antitumor effect was a 49% reduction in enhancing tumor volume. In Group A, 38% (3/8) of the tumors had decreased enhancing tumor volume of tumors compared to 9% (1/11) of Group B tumors. Therefore, the Group A dosing provided a therapeutic yet subcurative dose and this dosing was used for subsequent Y90 infusions to allow a measurable additional therapeutic effect of DEBIRI in the combination group.

### Radioembolization and $^{90}$Y Dosimetry

Mean fluoroscopy time (± SD) was 5.6 ± 3.7 min for Y90+DEBIRI versus 3.1 ± 1.7 min for Y90 only. Technically successful radioembolization was accomplished in all cases and all rabbits survived the procedure. Antegrade flow was preserved after radioembolization and delivery of DEBIRI microspheres was technically successful in 100% of cases (7/7) following Y90. Complete stasis after DEBIRI infusions was observed in 0% (0/10) of the survived rabbits and 7.7% (1/13), overall. Infusion in the left hepatic artery was possible in 29% (2/7) of Y90+DEBIRI rabbits and 38% (3/8) of Y90 rabbits with proper hepatic arterial delivery in all remaining rabbits. The mean calibrated vial activity was 1.0 ± 0.1 GBq.

Residual vial activity was 11.3 ± 4.2%. The lung shunt fraction (LSF) was estimated with hand-held survey meter with a mean LSF of 4.0 ± 6.5%. The mean absorbed dose for the Y90 and Y90+DEBIRI groups was similar at 54.2 ± 10.4 Gy and 54.9 ± 9.5 Gy, respectively.

## Laboratory Toxicity

Laboratory trends over time are shown in Figure 3. Early mild elevation in liver enzymes after radioembolization was common.

**At baseline (day 0):** Only albumin significantly differed (p=0.03) among treatment groups. Post hoc analysis showed the Y90 group had significantly lower baseline albumin level than either the Control or Y90+DEBIRI groups (p=0.013).

**At day 1:** ALT (p=0.05) and AST (p<0.01) showed significant differences among treatment groups. All treatment groups (Y90, DEBIRI, and Y90+DEBIRI) had significantly higher ALT and AST than the Control group. The Y90+DEBIRI group had significantly higher ALT (p=0.029) and AST (p=0.008) than the Y90 group.

**At days 3 and 7:** ALT significantly differed among treatment groups (p=0.03 for both). The treatment groups (Y90, DEBIRI, and Y90+DEBIRI) had significantly higher ALT than the Control group (day 3: p=0.004, p=0.020, and p= 0.009, respectively; day 7: p=0.013, p=0.029, and p=0.004, respectively). The Y90+DEBIRI group had significantly higher ALT than the Y90 group at both 3 (p=0.026) and 7 days (p=0.019).

**At day 14:** There were no longer significant differences between groups for any laboratory values.

## Tumor Volumes and CE-MRI

Representative T1w contrast-enhanced and T2w MR images from each group are shown in Figure 4. Waterfall plots demonstrating percent change in imaging volume measurements from baseline to 2 weeks are shown in Figure 5. Imaging volume measurements of TV and ETV at baseline and 2-weeks are shown in Figure 6.

**At baseline (week 0),—**no significant differences were observed between groups in total tumor volume (TV, p=0.960) or enhancing tumor volume (ETV, p=0.882).

**TV:** The Y90+DEBIRI group was the only treatment to show statistically significant decrease in tumor volume at 2 weeks compared to the Control group (p=0.012) after Bonferroni post-hoc correction.

**ΔTV:** Both Y90+DEBIRI (p=0.002) and Y90 groups (p=0.014) showed significantly decreased change in tumor volume (ΔTV) in compared to the Control group after Bonferroni post-hoc correction.

**ETV:** There were no statistically significant differences in enhancing tumor among treatment groups at 2 weeks (p=0.064).

**ΔETV:** There was significantly different ΔETV among groups (p=0.025). However, the trend for decreased ΔETV in the Y90+DEBIRI group was no longer significant after Bonferroni post-hoc correction (p=0.070).

### Histology

Pathological findings using H&E and trichrome staining in the normal (non-tumor) liver tissue did not demonstrate congestion or fibrosis. By ANOVA testing, there were no significant difference observed among different groups in tumor area (TA, p=0.48), viable area (VA, p=0.05), or viable area percentages (VA%, p=0.41) analyzed on H&E.

## DISCUSSION

This study investigated the combination intra-arterial radio- and chemoembolization microspheres in the rabbit VX2 model. The primary outcomes of interest were feasibility (i.e. technical success) and toxicity. Tumor imaging volumetrics and histology were also assessed. The addition of DEBIRI chemoembolization after Y90 radioembolization was technically successful in all cases and added 2.5 minutes to the total fluoroscopy time compared to Y90 alone. After early elevation in liver enzymes with ALT peaking at 2–3d and AST peaking at 1–2d, these laboratory values normalized quickly and were similar among all groups by 14d. Imaging at 2 weeks showed the Y90+DEBIRI group was the only treatment group to show statistically significant reductions in tumor volume on imaging compared to those of the Control group (p=0.012).

With demonstrated safety in phase III trials early in the treatment of liver-dominant mCRC, there is a need to further optimize Y90 treatments to improve efficacy for these patients (21,22). Irinotecan has an established survival and quality of life benefit in mCRC (23,24). Van Hazel et al explored the use of systemic irinotecan concomitant to radioembolization administered on the first week of therapy in a dose-escalation study in patients who failed fluorouracil-based chemotherapy with no maximum-tolerated dose reached at 100mg/m$^2$ delivered on days 1 and 8 of a 3 week cycle (25). Liver-directed therapy with DEBIRI chemoembolization is now an area of active investigation in phase III clinical trials (13–15,26,27). DEBIRI delivers high tumor drug concentrations with specificity that is not achieved with IV or intra-arterial administrations (28,29). Since irinotecan relies on hepatic parenchyma adjacent to tumor tissues for conversion to its active form (SN-38), the preservation of nearby hepatic parenchyma is essential. Therefore, the timing of irinotecan delivery should precede therapies that are physically destructive to the tumor and normal parenchyma interface (i.e. radiofrequency or microwave ablation). In the present study, the concomitant delivery of Y90 with DEBIRI microspheres required minimal additional time, had additive laboratory toxicity that resolved by two weeks, and resulted in enhanced antitumor activity.

Y90 radioembolization delivers high radiation dose in the vicinity of the microspheres but less vascular regions of the tumor may not receive sufficient levels of radiation (30). Irinotecan is already included in the treatment paradigm for mCRC. Although not typically employed as a radiosensitizer in clinical practice, irinotecan has radiosensitizing effects that may act through cell cycle arrest (31,32). The combination of a well-transported

radiosensitizer (e.g., irinotecan), to access less vascular regions of the tumor, may improve anti-tumor therapy by sensitizing these cells to a lower dose of radiation. Furthermore, irinotecan may have direct cytotoxic effects on cells not killed through radiation effects, potentially improving therapy. Further studies are required to elucidate the therapeutic mechanisms of Y90+DEBIRI.

### Limitations.

The VX2 model allows pilot studies for intra-arterial therapies because the tumor blood supply is almost entirely derived from the hepatic artery (33) but it is not an appropriate surrogate for therapeutic response in colorectal liver metastases. While transgenic mouse models of colon cancer have been historically useful, they limit technical interventions due to the small anatomy and larger models may be necessary for larger anatomy that may translate more closely (34–36). We used a fixed, subcurative dose in Y90 and DEBIRI groups to examine the interaction between these two therapies and benefits of combination therapy at therapeutic dosing levels remain unknown. DEBIRI microsphere treatment after Y90 had an improved treatment effect but we did not define whether this improvement was explained by irinotecan or the embolic effect of the microspheres or if Y90 influenced the levels of SN-38 within normal hepatic parenchyma or tumor. Including groups with bland embolization and bland embolization+Y90 could inform these relationships but this was beyond the scope of the present study. Additional studies are needed to better define the therapeutic mechanism for Y90+DEBIRI. Lastly, future work implementing $^{90}$Y PET/CT or PET/MRI imaging techniques to visualize microsphere distributions and dosimetry could advance our understanding of these relationships.

## CONCLUSION

Rabbits with multifocal intrahepatic VX2 tumors were treated with subcurative dosing for both Y90 and DEBIRI. Combination therapy with Y90+DEBIRI was feasible and safe with demonstrated enhanced antitumor effect in the rabbit VX2 model. This combined approach warrants further investigation.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Abbreviations

| | |
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| **ALP** | alkaline phosphatase |
| **ALT** | alanine transaminase |
| **ANOVA** | analysis of variance |
| **AST** | aspartate transaminase |
| **CE** | contrast enhanced |
| **DSA** | digital subtraction angiography |
| **DEBIRI** | drug-eluting beads loaded with irinotecan chemoembolization |
| **ETV** | enhancing tumor volume (imaging) |
| **ETV%** | enhancing tumor volume percentage (imaging) |
| **H&E** | hematoxylin and eosin |
| **IV** | intravenous |
| **LFTs** | liver function tests |
| **MRI** | magnetic resonance imaging |
| **NA** | necrotic area (pathology) |
| **NTV** | non-enhancing tumor volume (imaging) |
| **ROI** | regions-of-interest |
| **T1W** | T1-weighted MRI |
| **TACE** | transarterial chemoembolization |
| **TA** | overall tumor area (pathology) |
| **TV** | tumor volume (imaging) |
| **VA** | viable tumor area (pathology) |
| **VA%** | percentage of tumor that is viable (pathology) |
| **Y90** | yttrium-90 radioembolization |

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**Key Points:**

1) It is technically feasible to intra-arterially deliver Irinotecan drug eluting microspheres directly after $^{90}$Y radioembolization microspheres. 2) The combination therapy had antitumor activity by MRI while either therapy alone did not control the local progression of disease. 3) No histologic differences were observed for viable area percentages and tumor area.

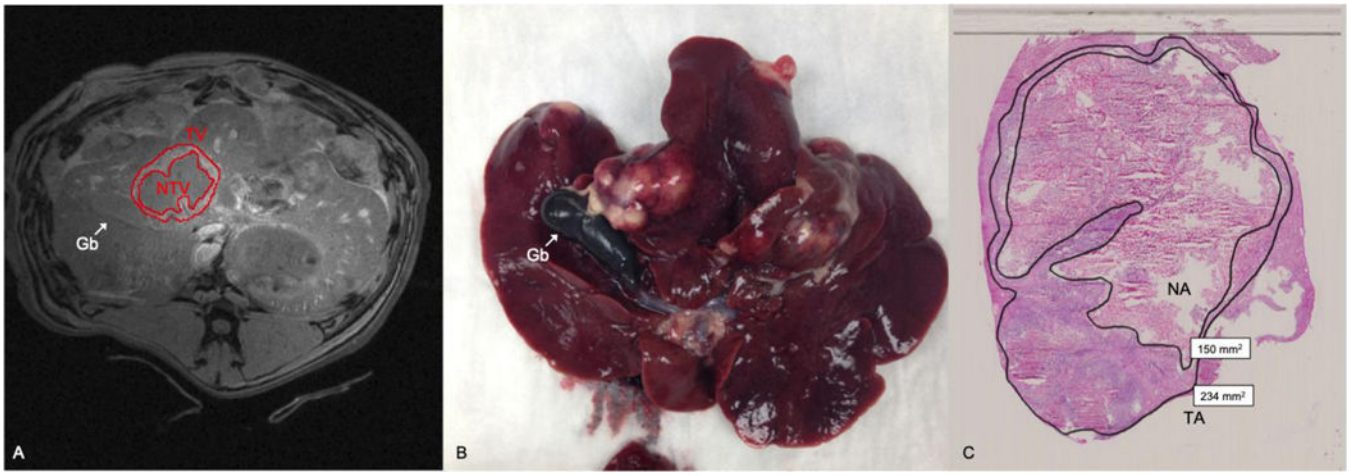


**Figure 1.**

(A) Contrast-enhanced T1W MRI demonstrates an enhancing tumor adjacent to the gallbladder (Gb) in this Y90-treated rabbit. The tumor volume (TV) was contoured along the outer margin of the enhancing tumor while the non-enhancing tumor volume (NTV) was contoured along the inner margin to encompass non-enhancing tumor that was isointense relative to the adjacent liver. (B) Gross pathology on liver explantation demonstrated a necrotic tumor adjacent to the gallbladder (Gb). (C) H&E staining of the tumor was used to define the overall tumor area (TA) taken as the outer margin of VX2 cell clusters and the necrotic area (NA) consisting of acellular material and proteinaceous debris abutting the inner layer of VX2 cells.

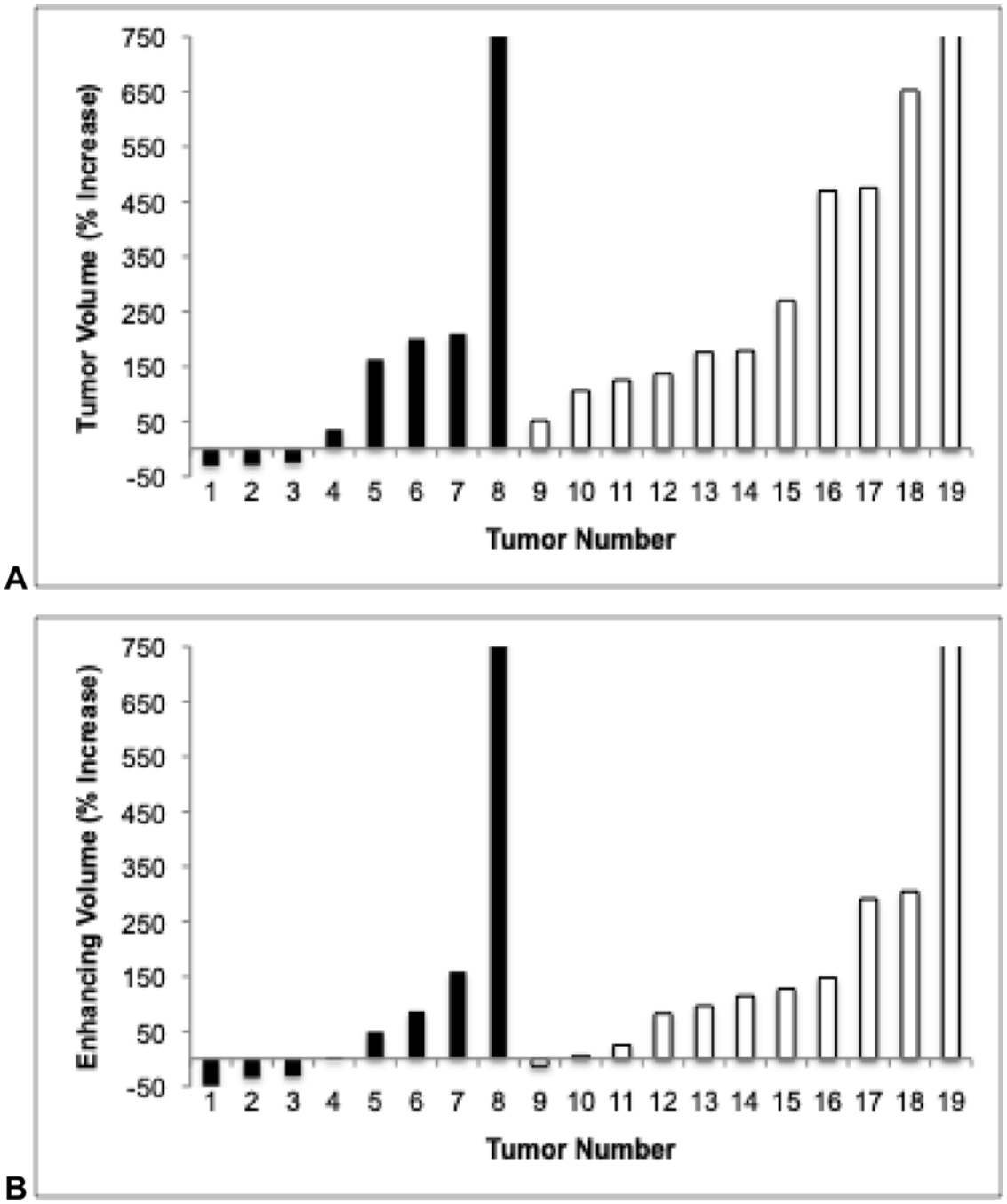


**Figure 2.**

(A) Waterfall plots demonstrating tumor volume (TV) changes from baseline imaging to imaging at 2 weeks in Group A (High Dose, black bars ■) versus Group B (Low Dose, open bars □) rabbits treated with Y90. Negative values denote decreased tumor size at 2 weeks. Group A demonstrated decreased tumor volume in 38% (3/8) tumors where no tumor in Group B had decreased volume at 2 weeks. (B) Group A dosing resulted in enhancing tumor volume (ETV) reduction in 50% of tumors (4/8) versus 9% of tumors (1/11) with Group B

dosing. Therefore, Group A dosing was selected for future studies as a therapeutic but subcurative Y90 dose.

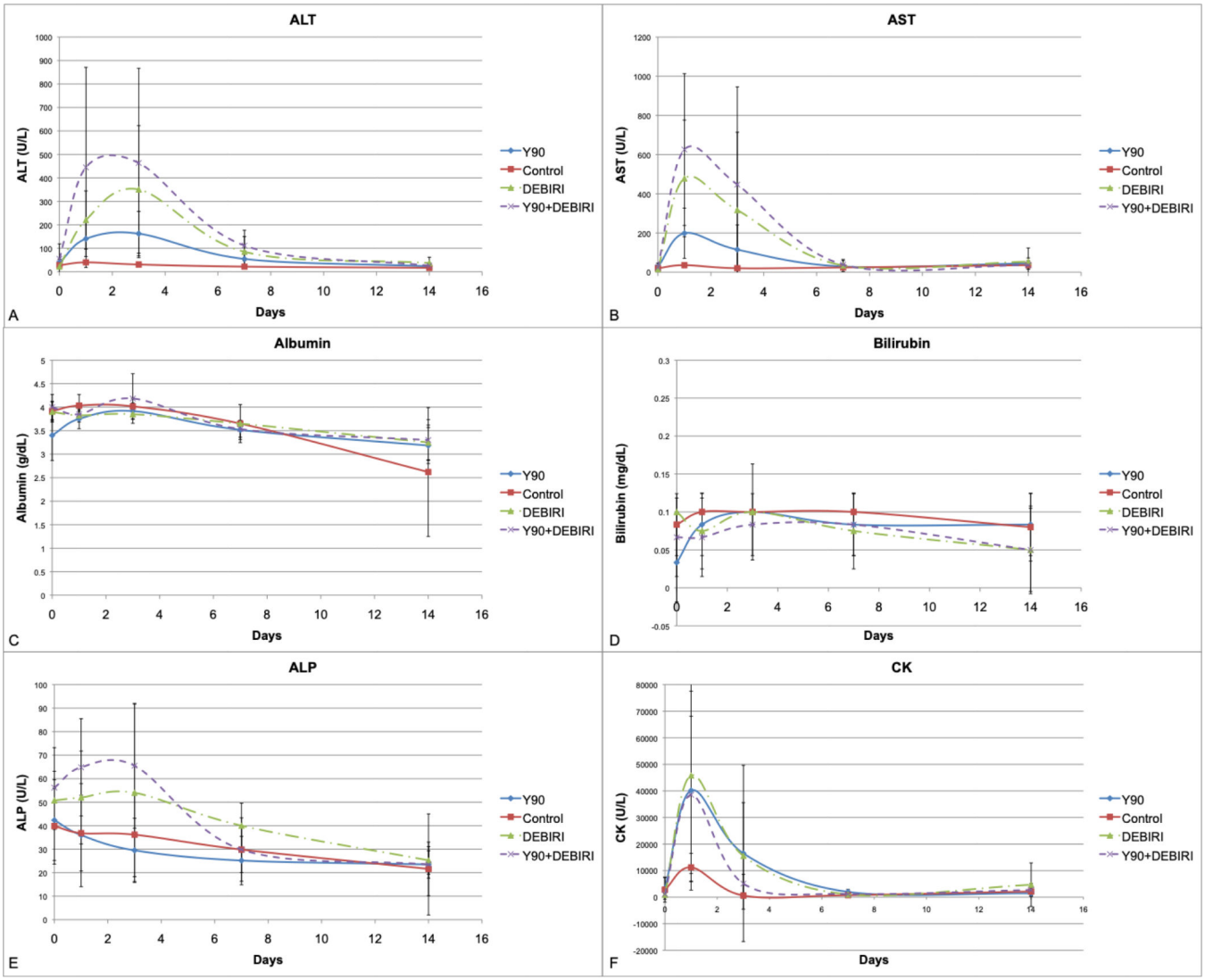


**Figure 3.**

Laboratory toxicities after treatment over the 2 week study period: (A) ALT, (B) AST, (C) Albumin, (D) Total Bilirubin, (E) ALP (F) CK.

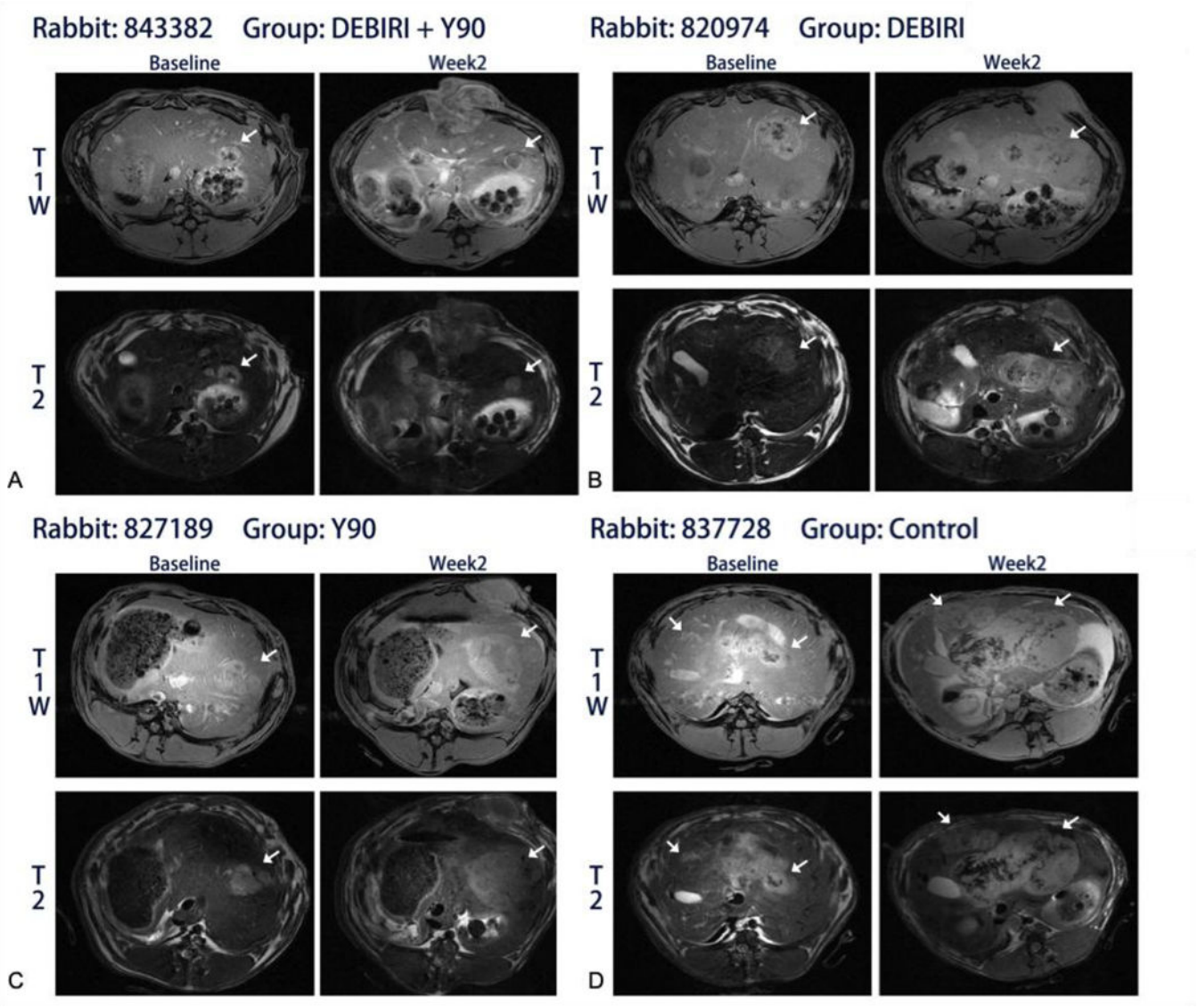


**Figure 4.**

MRI findings on contrast-enhanced T1W and T2W images. (A) Y90+DEBIRI. (B) DEBIRI treatment effects observed at 2-weeks included increased necrosis with thinned layers of rim enhancement along the margin of the tumor. (C) Y90 treatment group. (D) Control group with characteristic enhancement on T1w-MRI, hyperintensity on T2w images, and large central areas of necrosis with thick viable tumor periphery.

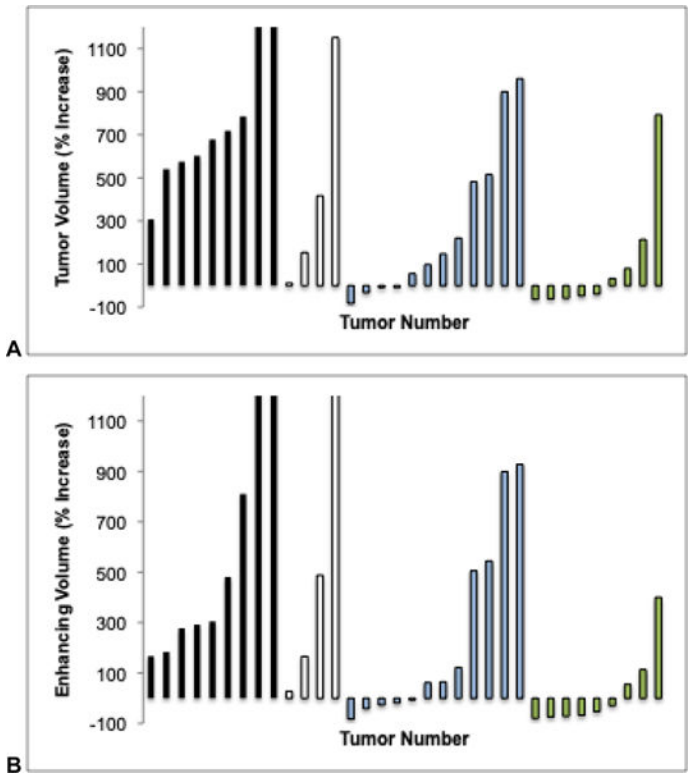


**Figure 5.**

Waterfall plots demonstrating (A) tumor volume (TV) changes and (B) enhancing tumor volume (ETV) changes from baseline imaging to imaging at 2 weeks (left to right) in the Control (black bars ■), DEBIRI (open bars □), Y90 (blue bars, ■), and Y90+DEBIRI Groups (green bars, ■). Negative values denote decreased tumor size at 2 weeks. The Y90 and Y90+DEBIRI groups were the only groups to demonstrate decreased TV and/or ETV at 2 weeks. The addition of DEBIRI to Y90 in the Y90+DEBIRI group resulted in decreased TV in 55.6% (5/9) versus 33.3% (4/12) and decreased ETV in 66.7% (6/9) versus 41.7% (5/12) in comparison to Y90 alone.

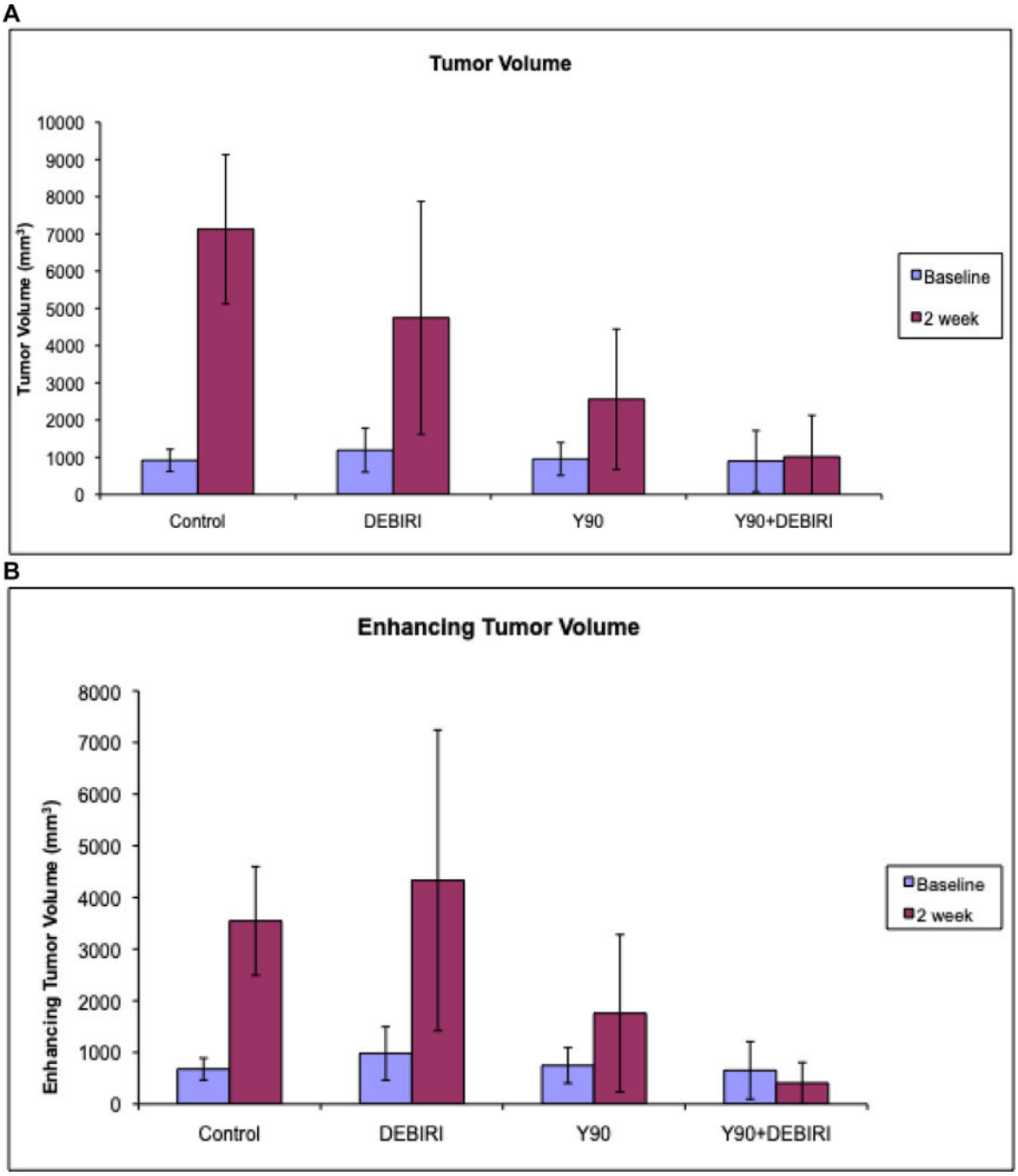


**Figure 6.**

MRI measurements of tumor volumes (TV) and enhancing tumor volumes (ETV). Error bars represent SD. (A) TV was significantly reduced in the Y90+DEBIRI group compared to the Control group (p=0.012). (B) ETV was not significantly different among groups.

**Table 1.**

Y90 Administered Activities

| Administered Activity (mCi) | Mean | SD | Minimum | Maximum |
|---|---|---|---|---|
| Y90 | 2.21 | 0.24 | 1.88 | 2.49 |
| Y90+DEBIRI | 2.46 | 0.18 | 2.18 | 2.73 |

DEBIRI = drug-eluting beads loaded with irinotecan chemoembolization, SD = standard deviation; Y90 = yttrium-90 radioembolization