Memorial Sloan Kettering Cancer Center

Aspirin improves liver function and survival after TAE of HCC

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Disclosures

Financial disclosures

Ed Boas is a co-founder of Claripacs, LLC. He received research supplies from Bayer (sorafenib). He is an investor in Labdoor, Qventus, CloudMedx, and Notable Labs. He is the inventor and assignee of US patent 8233586.

Off-label use of medications will be discussed.

Adjuvants for locoregional therapy

Problems with current therapy:

- High rate of recurrence after TACE / TAE.
- On average, only 65% of the tumor is necrotic after TACE of HCC smaller than 5 cm.
- Only 43% of individual lesions showed complete necrosis on histology.

Reference: Golfieri R, et al (2011). *Hepatology* 53: 1580-9.

Adjuvants for locoregional therapy

Escape mechanisms that allow tumor cells to survive TACE / TAE:

- Immune tolerance to necrotic tumor
- Ischemia-induced angiogenesis
- Increased anaerobic respiration

Possible solution:

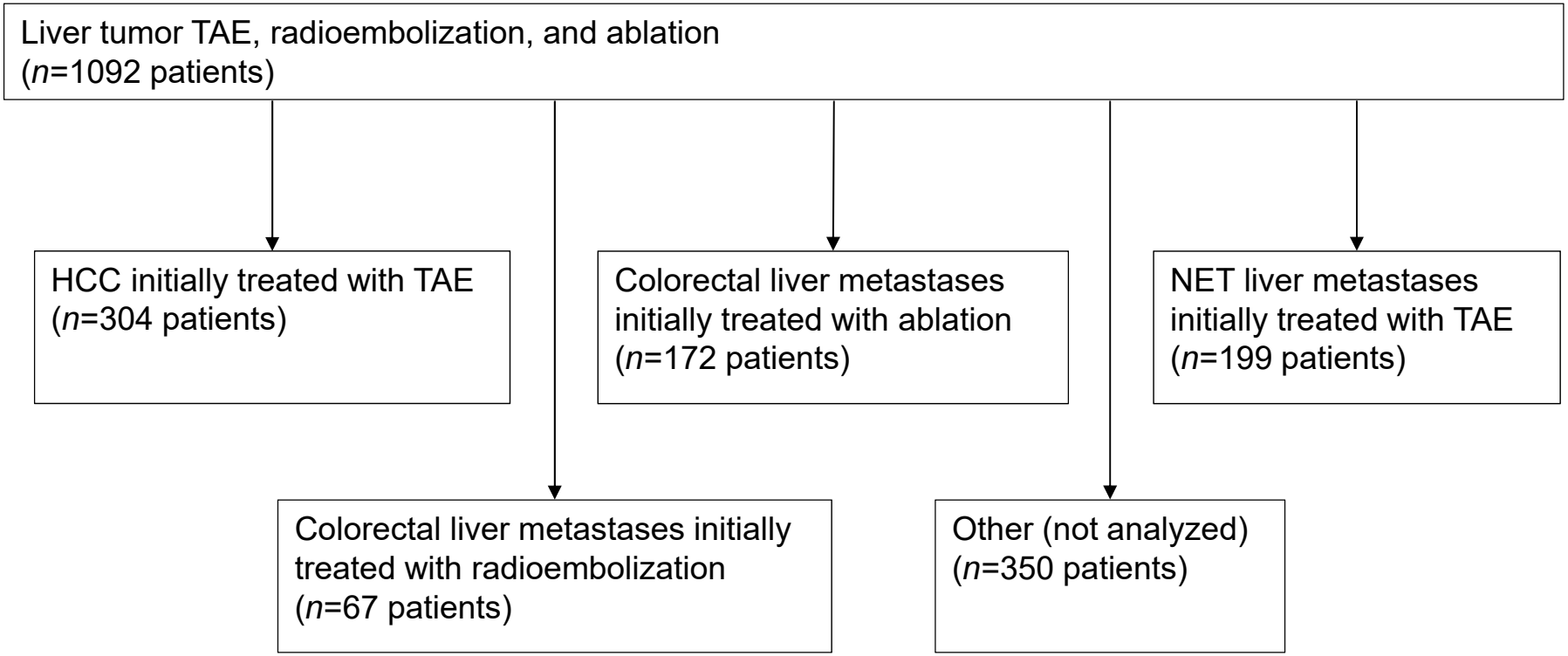
Several FDA-approved medications block these escape mechanisms.

Goal: Find new adjuvant medications

- Determine if outpatient medications taken at the time of liver tumor embolization or ablation affect survival.

- Examine prescription and non-prescription medications, taken for reasons unrelated to the primary cancer diagnosis.

Treatment groups



543 different medications taken at time of locoregional therapy

abiraterone
acarbose
acebutolol
acenocoumarol
acetaminophen
acetaZOLAMIDE
acetylcysteine
acrivastine
acyclovir
adalimumab
ado-trastuzumab emtansine
Al hydroxide
albuterol
alclometasone topical
alendronate
alfuzosin
aliricumab
aliskiren
allopurinol
alpha-lipoic acid
ALPRAZolam
amantadine
aMILoride
amiodarone
amitriptyline
amLODIPine
ammonium lactate topical
amoxicillin
amphetamine
anastrozole
apixaban
aprepitant
ARIPiprazole
ascorbic acid
aspirin
atenolol
atorvastatin
atovaquone
atropine
azelastine nasal
azilsartan
azithromycin
bacitracin topical
baclofen
beclomethasone
benazepril
benzonatate
benzoyl peroxide topical
besifloxacin ophthalmic
betamethasone topical
bicalutamide
bifidobacterium
bifidobacterium infantis
bimatoprost ophthalmic
biotin
bisacodyl
bismuth subsalicylate
bisoprolol
bortezomib
brimonidine ophthalmic
brinzolamide ophthalmic
bromfenac ophthalmic
brompheniramine
budesonide
bumetanide
buPROPion
cabergoline
cabozantinib
caffeine
calamine topical
calcitriol
calcium
calcium acetate
calcium carbonate
calcium citrate
calcium lactate
canagliflozin
candesartan
capecitabine
carBAMazepine
carbidopa
carbonyl iron
carteolol ophthalmic
carvedilol
cefadroxil
cefdinir
cefepime
cefTRIAXone
cefuroxime
celecoxib
cephalexin
cetirizine
chlorhexidine topical
chlorthalidone
cholecalciferol
cholestyramine
chondroitin
ciclesonide nasal
ciclopirox topical
cilostazol
cimetidine
cinacalcet
cinnamon
ciprofloxacin
ciprofloxacin otic
citalopram
citric acid
clarithromycin
clavulanate
clindamycin
clindamycin topical
clobetasol topical
clonazePAM
cloNIDine
clopidogrel
clotrimazole
clotrimazole topical
codeine
colchicine
colesevelam
colestipol
conjugated estrogens
conjugated estrogens topical
cranberry
crizotinib
cyanocobalamin
cyclobenzaprine
cyclopentolate ophthalmic
cycloSPORINE ophthalmic
cyproheptadine
dabigatran
dalteparin
dapsone
dapsone topical
DAPTOmycin
darunavir
dehydroepiandrosterone
denosumab
desonide topical
desvenlafaxine
dexamethasone
dexamethasone ophthalmic
dexamethasone otic
dexlansoprazole
dextroamphetamine
dextromethorphan
diazepam
diclofenac
diclofenac topical
dicyclomine
diflorasone topical
digoxin
diltiazem
diltiazem cream
diphenhydrAMINE
diphenoxylate
docusate
dofetilide
dolutegravir
donepezil
dorzolamide ophthalmic
doxazosin
doxycycline
dronabinol
drospirenone
DULoxetine
dutasteride
efavirenz
emollients, topical
emtricitabine
enalapril
enoxaparin
entecavir
eplerenone
epoetin alfa
ergocalciferol
erlotinib
ertapenem
erythromycin ophthalmic
escitalopram
esomeprazole
estradiol
estradiol topical
eszopiclone
etanercept
ethinyl estradiol
everolimus
exemestane
ezetimibe
famotidine
febuxostat
fenofibrate
fentaNYL
ferrous fumarate
ferrous gluconate
ferrous sulfate
fexofenadine
filgrastim
finasteride
flax
fluconazole
fludrocortisone
fluocinolone topical
fluocinonide topical
fluorometholone ophthalmic
FLUoxetine
flurazepam
fluticasone
fluticasone nasal
fluvoxaMINE
folic acid
fondaparinux
formoterol
furosemide
gabapentin
garlic
gemfibrozil
gentamicin ophthalmic
gentamicin topical
glimepiride
glipiZIDE
glucagon
glucosamine
glucose
glutamine
glyBURIDE
granisetron
guaiFENesin
haloperidol
heparin
homatropine
hydrALAZINE
hydrochlorothiazide
HYDROcodone
hydrocortisone
hydrocortisone topical
HYDROmorphone
hydroquinone topical
hydroxypropyl methylcellulose ophthalmic
hydrOXYzine
hyoscyamine
ibandronate
ibuprofen
icosapent
imatinib
imiquimod topical
immune globulin intravenous
indomethacin
inFLIXimab
inositol
insulin
insulin aspart
insulin aspart protamine
insulin detemir
insulin glargine
insulin glulisine
insulin isophane
insulin isophane (NPH)
insulin lispro
insulin lispro protamine
insulin regular
ipratropium
ipratropium nasal
irbesartan
iron
iron polysaccharide
isosorbide dinitrate
isosorbide mononitrate
ISOtretinoin
itraconazole
ketoconazole
ketoconazole topical
ketorolac ophthalmic
labetalol
lactic acid topical
lactobacillus
lactobacillus acidophilus
lactulose
lamoTRIgine
lanreotide
lansoprazole
latanoprost ophthalmic
lecithin
ledipasvir
lenalidomide
letrozole
leuprolide
levalbuterol
levETIRAcetam
levocetirizine
levodopa
levofloxacin
levonorgestrel
levothyroxine
lidocaine
lidocaine topical
linaclotide
linezolid
liothyronine
liraglutide
lisdexamfetamine
lisinopril
loperamide
loratadine
LORazepam
losartan
loteprednol ophthalmic
lovastatin
lurasidone
lysine
magnesium chloride
magnesium citrate
magnesium gluconate
magnesium hydroxide
magnesium oxide
magnesium sulfate
maraviroc
mebendazole
meclizine
megestrol
melatonin
meloxicam
mercaptopurine
mesalamine
metaxalone
metFORMIN
methadone
methotrexate
methylphenidate
methylPREDNISolone
methylsulfonylmethane
metoclopramide
metolazone
metoprolol
metroNIDAZOLE
Mg hydroxide
micafungin
miconazole topical
midodrine
milk thistle
mineral oil
minocycline
minoxidil
minoxidil topical
mirabegron
mirtazapine
mitotane
modafinil
mometasone
mometasone nasal
montelukast
morphine
moxifloxacin
multivitamin
multivitamin with iron
multivitamin with minerals
mupirocin topical
nabumetone
nadolol
naproxen
nebivolol
neomycin
niacin
nicotine
NIFEdipine
nisoldipine
nitrofurantoin
nitroglycerin
norethindrone
nortriptyline
nystatin
nystatin topical
octreotide
ocular lubricant
OLANZapine
olmesartan
olopatadine ophthalmic
omega-3 polyunsaturated fatty acids
omeprazole
ondansetron
opium
orlistat
oseltamivir
oxacillin
oxaprozin
oxiconazole topical
oxybutynin
oxyCODONE
oxymorphone
PACLitaxel
PACLitaxel protein-bound
pancrelipase
pantoprazole
papaverine
paricalcitol
PARoxetine
PB
pegfilgrastim
penicillin G sodium
penicillin V potassium
pentoxifylline
permethrin topical
phenol topical
phenoxybenzamine
phentolamine
phenylephrine topical
phenytoin
pioglitazone
pirbuterol
pitavastatin
polycarbophil
polyethylene glycol 3350
polymyxin B ophthalmic
potassium chloride
potassium citrate
potassium gluconate
potassium phosphate
pramoxine topical
pravastatin
prednisoLONE
prednisoLONE ophthalmic
predniSONE
pregabalin
prilocaine topical
prochlorperazine
progesterone
propranolol
PSE
pseudoephedrine
psyllium
pyridoxine
QUEtiapine
quinapril
RABEprazole
raloxifene
raltegravir
ramipril
ranitidine
ranolazine
regorafenib
repaglinide
resveratrol
ribavirin
rifampin
rifaximin
rilpivirine
risedronate
ritonavir
rivaroxaban
rizatriptan
rosuvastatin
salicylic acid topical
salmeterol
saw palmetto
saxagliptin
scopolamine
selenium
senna
sertraline
sildenafil
silodosin
silver sulfADIAZINE topical
simeprevir
simethicone
simvastatin
sirolimus
sitaGLIPtin
sodium bicarbonate
sodium biphosphate
sodium chloride
sodium chloride nasal
sodium citrate
sodium hyaluronate topical
sodium phosphate
sofosbuvir
solifenacin
SORAfenib
sotalol
spironolactone
sucralfate
sulfamethoxazole
SUMAtriptan
SUNItinib
tadalafil
tamoxifen
tamsulosin
tapentadol
telmisartan
temazepam
temozolomide
tenofovir
terazosin
terbutaline
testosterone
tetrahydrozoline ophthalmic
thiamine
thyroid desiccated
timolol ophthalmic
tiotropium
tiZANidine
tobramycin ophthalmic
tofacitinib
topiramate
torsemide
traMADol
trastuzumab
travoprost ophthalmic
traZODone
tretinoin topical
triamcinolone nasal
triamcinolone topical
triamterene
trimethoprim
trimethoprim ophthalmic
triprolidine
tropicamide ophthalmic
ubiquinone
urea topical
ursodiol
valACYclovir
valGANciclovir
valsartan
vancomycin
vandetanib
vardenafil
varenicline
vedolizumab
vemurafenib
venlafaxine
verapamil
vilanterol
vilazodone
vinorelbine
vitamin A
vitamin A & D topical
vitamin D
vitamin E
warfarin
witch hazel topical
zinc oxide topical
zinc sulfate
zoledronic acid
zolpidem

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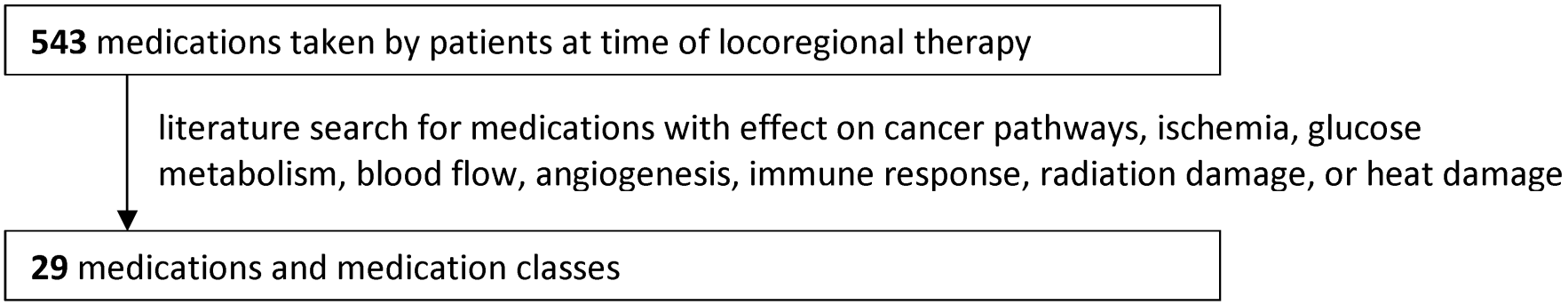
Medications that might improve locoregional therapy



Examples of medication classes

Immunomodulatory
- aspirin (116 patients)
- other NSAIDs (106 patients)
- corticosteroids (68 patients)
- other immunosuppressants (20)
- G-CSF (21 patients)
- antiviral for hepatitis B or C (26)

Glucose metabolism
- insulin (59 patients)
- metformin (52 patients)
- other oral anti-diabetic agents (55)

Blood flow
- beta blocker (156 patients)
- calcium channel blocker (108)
- ACE inhibitor / ARB (144 patients)
- diuretic (138 patients)

Radioprotective
- anticoagulant (80 patients)
- NSAID
- corticosteroid (68 patients)
- ursodiol (43 patients)
- vitamin C (33 patients)

Methods

Treatment groups

HCC TAE	Colorectal ablation	Colorectal Y90	NET TAE

29 medications and medication classes

- statin
- beta blocker
- CCB
- ACE inhibitor / ARB
- diuretic
- anticoagulant
- anti-platelet
- aspirin
- NSAID (excluding aspirin)
- corticosteroids
- non-corticosteroid immunosuppressant
- G-CSF
- antiviral (anti-hepatitis B/C)
- antiviral (not anti-hepatitis B/C)
- any antiviral
- any antibiotic
- metformin
- non-metformin oral antidiabetic agents
- insulin
- PPI
- gabapentin
- ursodiol
- levothyroxine
- iron
- omega-3 polyunsaturated fatty acids
- folic acid
- cyanocobalamin
- vitamin C
- vitamin D

For patients taking versus not taking each medication, calculate:

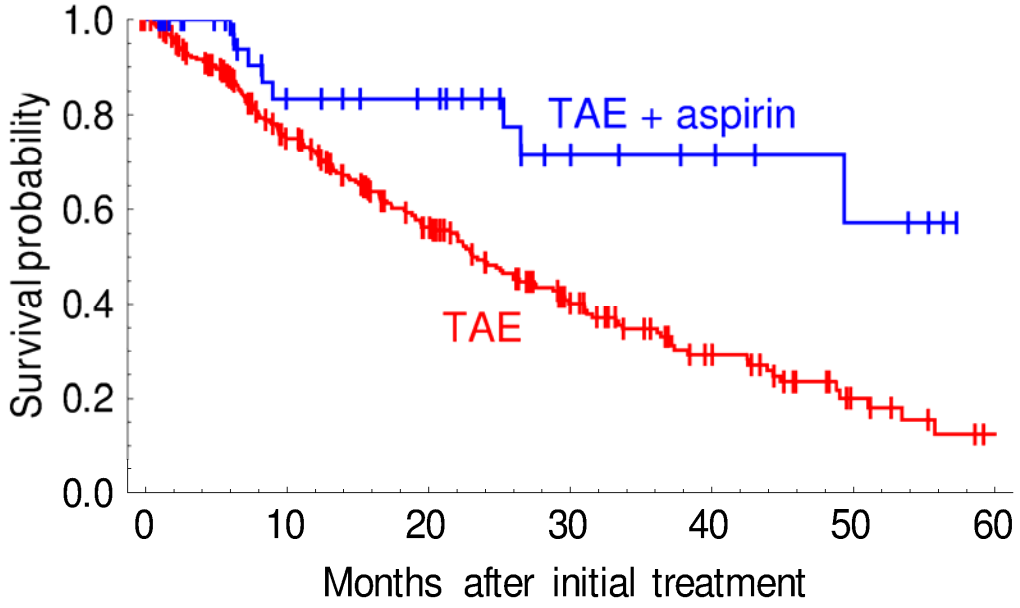
- Kaplan Meier curves
- Patient characteristics: AJCC stage, Child Pugh score, comorbidities, ECOG status

Results: Medications that improve survival after locoregional therapy

HCC TAE	Colorectal ablation	Colorectal Y90	NET TAE
Beta blocker **Aspirin** Other NSAIDs Antiviral (hep B/C) PPI	Beta blocker	(none)	(none)

Bold medications remain statistically significant after Bonferroni correction for multiple comparisons ($p < 0.0017$).

Results: Survival after TAE of HCC



n = 304 patients
p = 0.0008

Number at risk							
TAE:	262	168	108	56	29	10	2
TAE + aspirin:	42	23	19	10	7	4	0

Results: Confounding variables

For patients taking versus not taking aspirin or beta blockers at the time of TAE, there was **no difference in**:

- AJCC stage
- Child Pugh score
- underlying liver disease
- ECOG performance status
- Charlson comorbidity index
- prior sorafenib
- prior liver resection
- selectivity of the embolization

Aspirin and cancer

- Chronic inflammation plays a key role in cancer development, and this can be blocked by NSAIDS (Weinberg 2014).

- Large randomized trials have shown that aspirin reduces death from colorectal cancer, pancreatic cancer, and other adenocarcinomas (Rothwell 2011).

References:

- Weinberg RA. (2014) *The Biology of Cancer*. 2nd ed.
- Rothwell PM et al. (2011) *Lancet.* 377(9759): 31-41.

Aspirin mechanisms

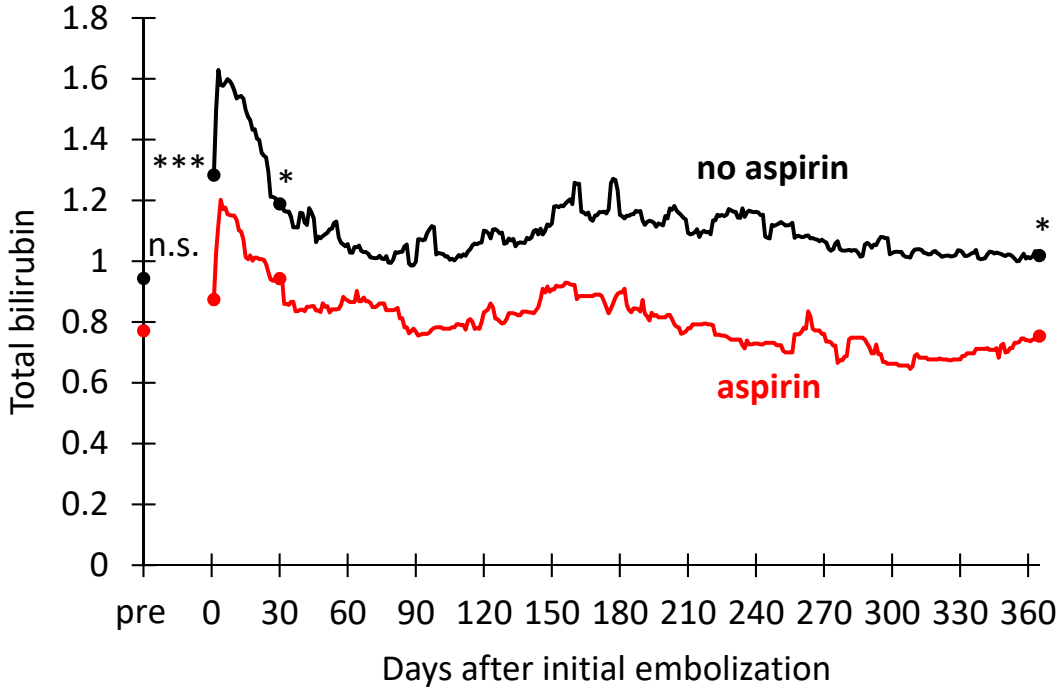
- **Anti-inflammatory**: Aspirin reduces death from chronic liver disease, and reduces development of new HCC.
- **Anti-angiogenic**: Aspirin inhibits hypoxia-induced angiogenesis.
- **Anti-glycolytic**: Aspirin inhibits phosphofructokinase, decreases glucose consumption by tumor cells, and decreases viability of tumor cells.

Aspirin mechanisms

HCC patients treated with TAE:

	Aspirin (*n*=42)	No aspirin (*n*=262)	*p* value
Initial response (CR or PR)	88%	90%	0.6
Median time to progression	6.2 mo	5.2 mo	0.4
Initial site of progression (treated lesion / other liver lesion / extrahepatic lesion)	53% / 40% / 8%	48% / 42% / 11%	0.8
Progression at time of death	88%	89%	1

Aspirin and liver function



n.s. $p > 0.05$

* $p \leq 0.05$

** $p \leq 0.01$

*** $p \leq 0.001$

Aspirin and liver function

- Retrospective and animal studies show decreased liver fibrosis in patients / animals taking aspirin.

References

- Jiang ZG, et al. (2016) *Aliment Pharmacol Ther*. 43: 734-43.
- Sitia G, et al. (2012) *PNAS*. 109: E2165-72.

Conclusion

- Aspirin and other NSAIDs were associated with improved survival when taken at the time of embolization for HCC.
- Aspirin was not associated with survival differences after locoregional therapy for NET or colorectal liver metastases.
- Aspirin might be hepatoprotective.

Clinical bottom line

- Consider starting HCC patients on aspirin 81 mg daily before TAE or TACE. (Use caution if history of bleeding or peptic ulcers)
- Baby aspirin does not need to be held before arterial access.
- Beta blockers should be used as first line therapy for peri-procedural hypertension.

Acknowledgements

Citations:

- Boas FE, Ziv E, Yarmohammadi H, Brown KT, Erinjeri JP, Sofocleous CT, Harding JJ, Solomon SB. (2017) “Adjuvant medications that improve survival after locoregional therapy.” *Journal of Vascular and Interventional Radiology*. 28: 971-7.
- Boas FE, Brown KT, Ziv E, Yarmohammadi H, Sofocleous CT, Erinjeri JP, Harding JJ, Solomon SB. (2018) “Aspirin is associated with improved liver function after embolization of hepatocellular carcinoma.” Submitted to *Hepatology Research*.