Evidence, Status and Future of Vascular therapies in cancer treatment

DFIR , Nyborg, Denmark 2023

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Paradigms?
Where to start?

No Conflict of interests

“Begin at the beginning and go on till you come to the end: then stop.”

— Lewis Carroll, Alice in Wonderland

Rationale and Techniques

Indications and success criteria

Evidence for benefit & risk

New horizons

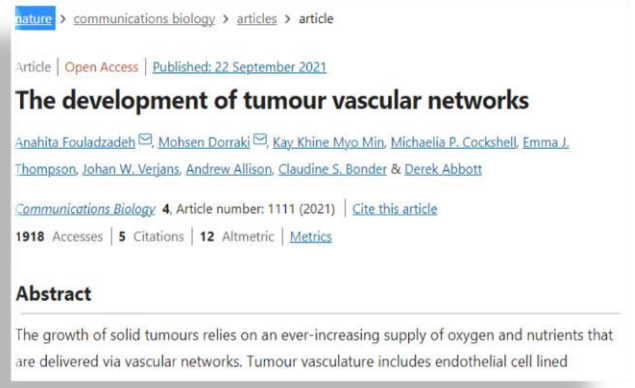
TECHNIQUE

Rationale for Intra-arterial therapies for cancer

Solid tumours cannot grow more than a few milimeters, without access to a blood supply. [1]

Neovascularization, is relatively uncommon in most normal tissues but is an essential feature of solid tumors (Folkman 2002)

Tumor Survival, Progression & Spread - depends firmly on vascular supply



nature › communications biology › articles › article

Article | Open Access | Published: 22 September 2021

The development of tumour vascular networks

Anahita Fouladzadeh, Mohsen Dorraki, Kay Khine Myo Min, Michaelia P. Cockshell, Emma J. Thompson, Johan W. Verjans, Andrew Allison, Claudine S. Bonder & Derek Abbott

Communications Biology 4, Article number: 1111 (2021) | Cite this article

1918 Accesses | 5 Citations | 12 Altmetric | Metrics

Abstract

The growth of solid tumours relies on an ever-increasing supply of oxygen and nutrients that are delivered via vascular networks. Tumour vasculature includes endothelial cell lined

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Author Manuscript
Cell Tissue Res. Author manuscript; available in PMC 2009 December 3.

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Cell Tissue Res. 2009 January ; 335(1): 241–248. doi:10.1007/s00441-008-0646-0.

Vascular targeted therapies in oncology

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Department of Experimental Clinical Oncology, Aarhus University Hospital, Aarhus, Denmark

Abstract

Neovascularization is intimately involved in tumor survival, progression, and spread, factors known to contribute significantly to treatment failures. Thus, strategies targeting the tumor blood vessel support network may offer not only unique therapeutic opportunities in their own right, but also novel means of enhancing the efficacies of conventional anticancer treatments. This article reviews one such therapeutic approach directed at the tumor blood vessel support network. Vascular disrupting therapies seek the destruction of the established neovasculature of actively growing tumors. The goal of these therapies is to cause a rapid and catastrophic shutdown in the vascular function of the tumor in order to arrest the blood flow and produce tumor cell death as a res deprivation and the build up of waste products.

1. Folkman J. What is the evidence that tumors are angiogenesis dependent? J Natl Cancer Inst. 1990 Jan 3;82(1):4-6. doi: 10.1093/jnci/82.1.4. PMID: 1688381.

Sushruta Samhita

Oldest medical text on surgery

CANCER IN ANCIENT INDIAN SURGERY

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Varanasi-221 005, India.

Received April 6, 1981 Accepted March 2

ABSTRACT: This paper contains some valid interpretations of the s explanations of the disease Cancer in terms of such relative diseases in Ayurveda. This is a result of a critical observation of the Susruta Samhita, followed by the translation of this authentic text of ancient Indian Surgery done by the author and his colleagues.

2500 years ago in the town of Varanasi, Suśruta, the Father of Surgery wrote his Saṁhitā, the classical Ayurvedic surgical treatise in Sanskrit.

To make its contents known to the modern scientists of the world its authentic, scientific, research-oriented syntax, English interpretation is being brought out as a monumental, encyclopaedic 12 volumes (over 5000 pages) Ancient Indian surgery series from the Institute of Medical Sciences, Banaras Hindu University.

Based on the above work some relevant excerpts on cancer and related matters in ancient Indian surgery are being given below.

1. Pathogenesis of Tumours (S. S. II. 11. 13-15/1)

The doṣas having got vitiated in any part of the body and afflicting the māmsa produce a swelling in the latter. This (lesion) is circular, fixed, slightly painful, big in size, broad based, slowly growing and does not suppurate; the same is called arbuda by the experts of this science. This is produced by (vitiated) vāta, pitta and kapha and by rakta and māmsa and also by medas. Its clinical features are always like that of granthi.

2. Blood-tumour (Raktārbuda) (S. S. II. 11. 15/2-17/1)

The vitiated doṣas compressing and contracting the śoṇita and vessels without undergoing suppuration and along with the discharge make the mascular lumps prominent. This is studded with fleshy buds and increases rapidly. This continuously discharges vitiated blood is incurable and is known as raktārbuda, because of the complication of haemorrhage the patient with this tumour becomes anaemic.

3. Muscle - Tumour (Māṁsārbuda) (S. S. II. 11. 17/2-19)

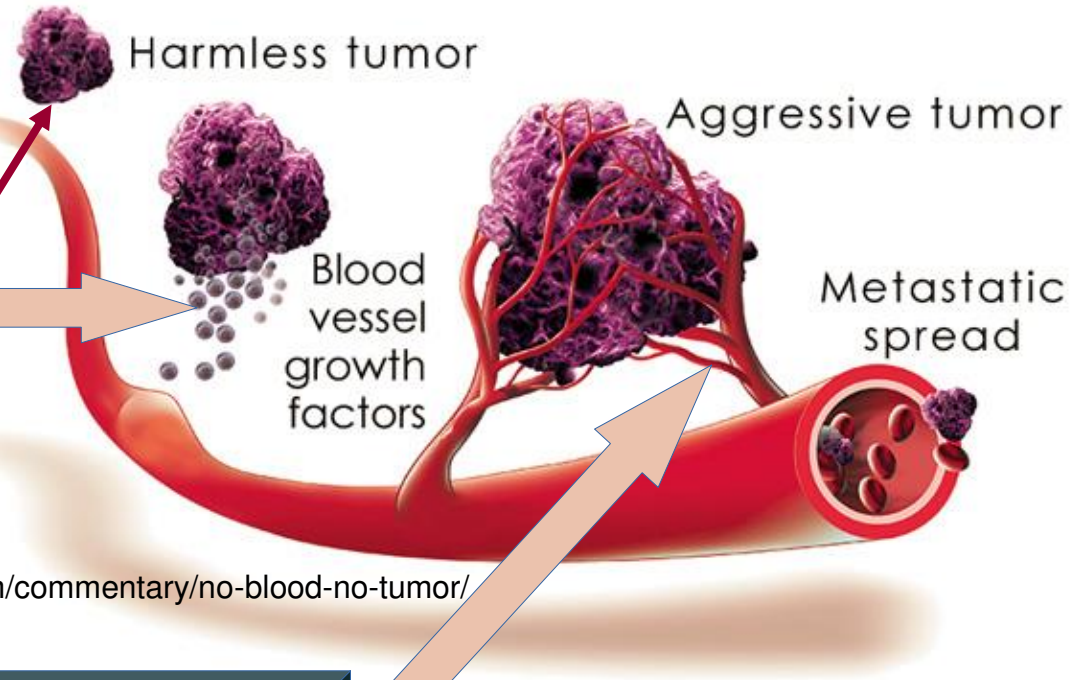
Due to fist blows, etc. the muscles of injured parts get vitiated and swollen. This is painless and smooth, is of the same colour (as skin), is non-suppurating, is like a stone and is fixed. This vitiated muscle increases much more in the non-vegetarian. This is māṁsārbuda and is said to be incurable. Even out of those which are curable, those which discharge, those situated over the vital parts over the srotasas and those which become fixed, should be discarded from treatment.

4. Multiple Tumours (S. S. II. 11. 21)

When another tumour grows over the pre-existing one, that is known adhyarbuda by the oncologist. When two tumours grow

Singhal GD. Cancer in ancient Indian surgery. Anc Sci Life. 1983 Jan;2(3):137-40. PMID: 22556969; PMCID: PMC3336753.

Angiogenesis - Growth Factors



https://phiab.com/commentary/no-blood-no-tumor/

Neovascularization

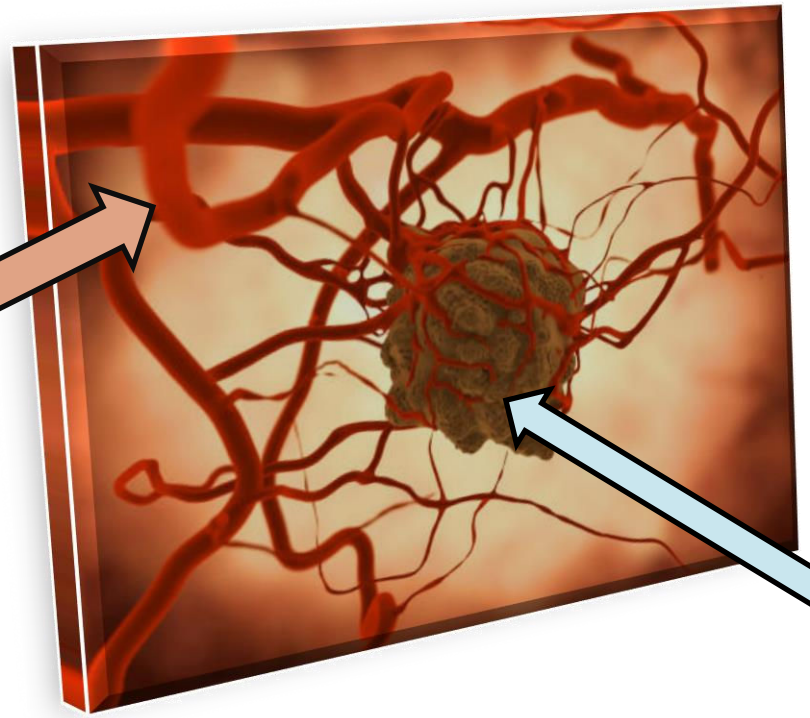
How does it happen?

Zuazo-Gaztelu I, Casanovas O. Unraveling the Role of Angiogenesis in Cancer Ecosystems. Front Oncol. 2018 Jul 2;8:248. doi: 10.3389/fonc.2018.00248. PMID: 30013950; PMCID: PMC6036108.

https://www.science.org/doi/10.1126/sciadv.abb0020

Rationale

Targeted through blood vessels



Normal Liver blood supply–
Portal ~ 75 to 80%
Arterial ~ 20 to 25%

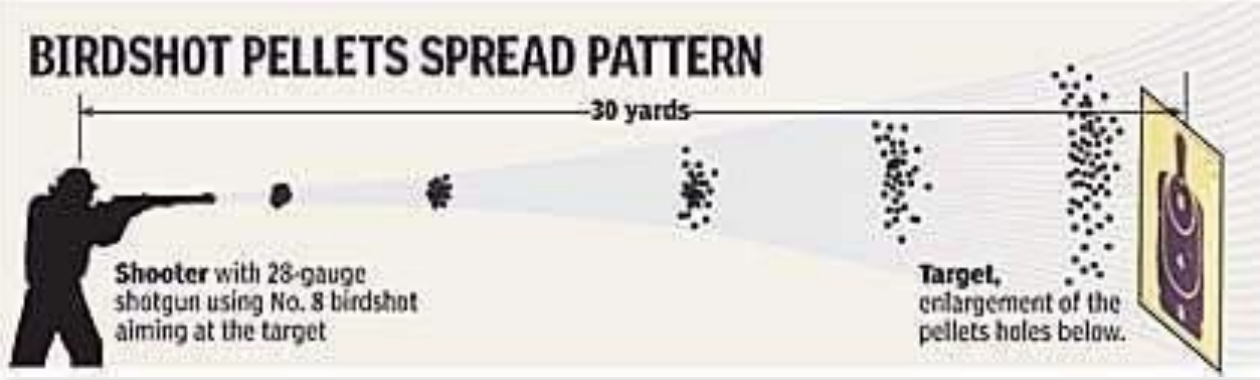
Hepatic Tumors - Almost exclusive supply by the hepatic artery

- Surgery
- RFA /MWA/ Cryo
- EBRT

https://medicalxpress.com/news/2018-06-blood-vessel-forming-cells-involved-aggressive.html

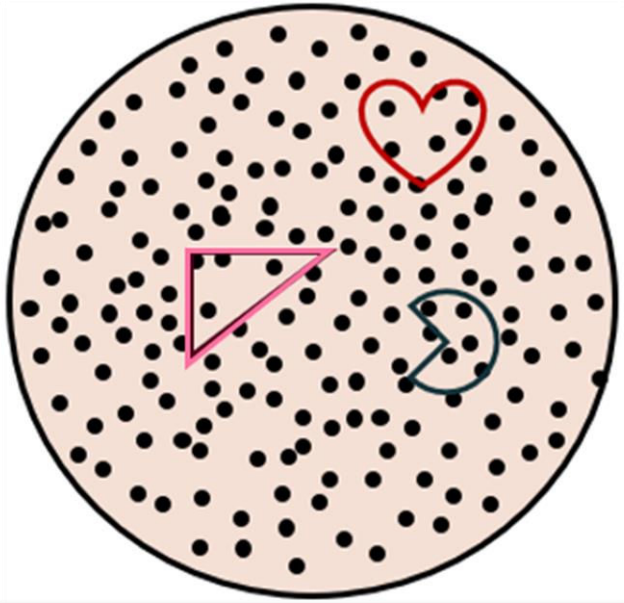
Rationale

Why Intra-arterial?



Poor selectivity - Suboptimal effect

Conventional anticancer systemic therapies



Low therapeutic Ratio - high side effects

Siemann DW, Horsman MR. Vascular targeted therapies in oncology. Cell Tissue Res. 2009 Jan;335(1):241-8. doi: 10.1007/s00441-008-0646-0. Epub 2008 Aug 28. PMID: 18752004; PMCID: PMC2788502.

IV Systemic Therapy

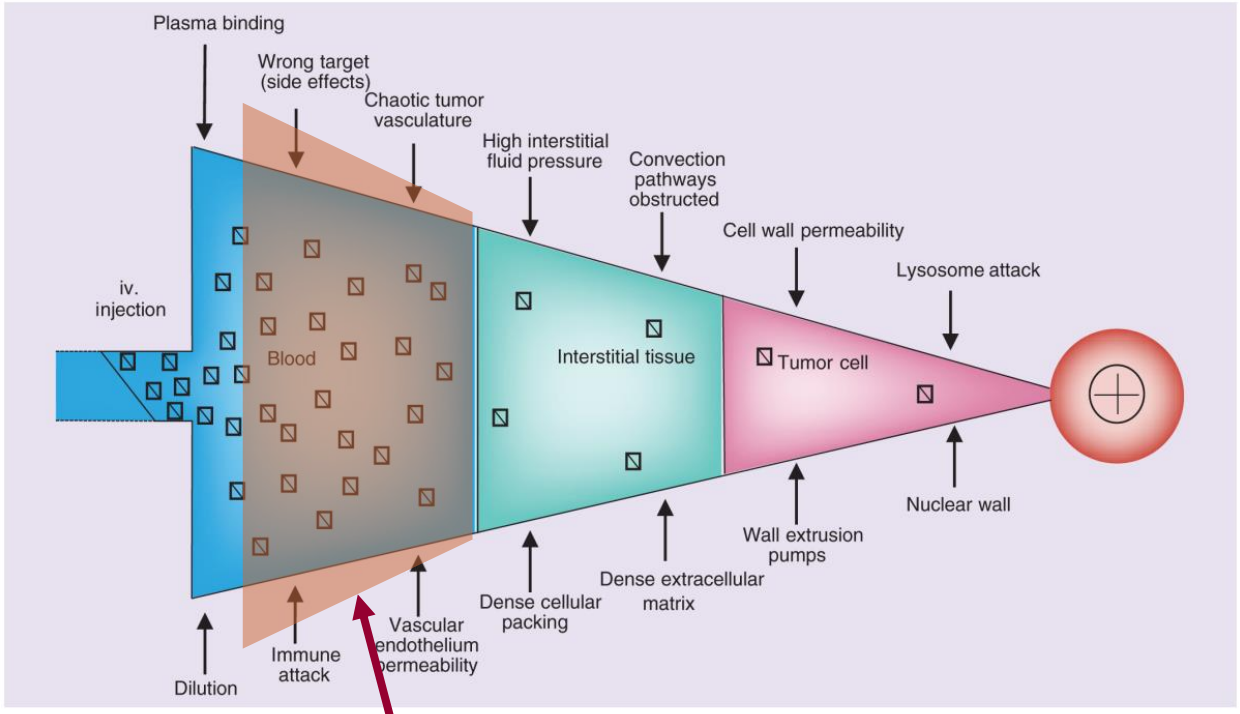
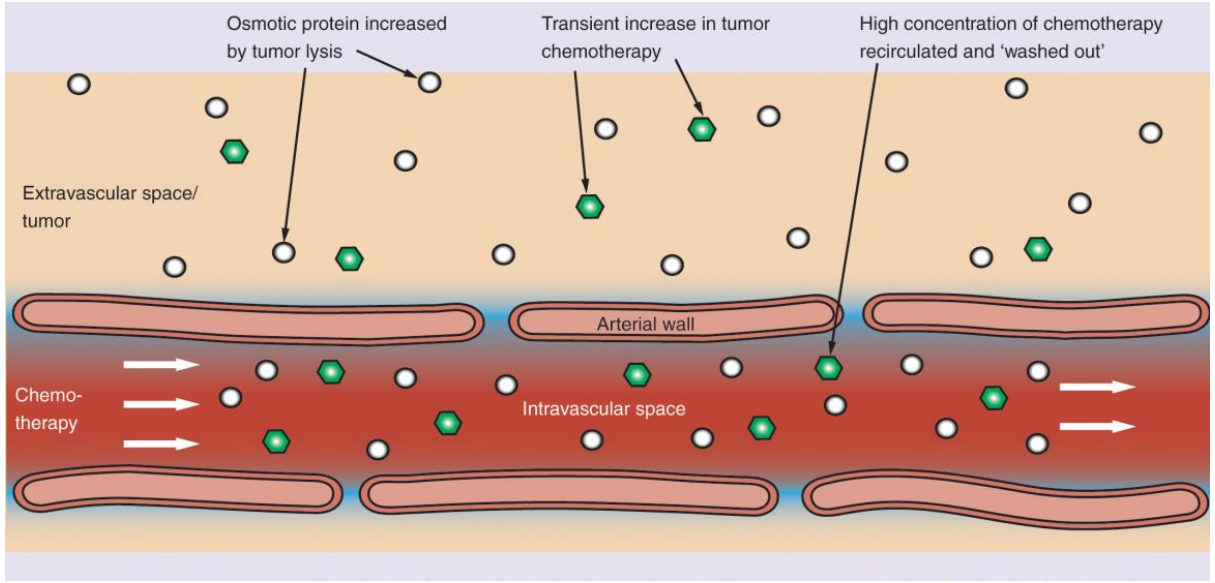


Figure 8. Standard intravenous chemotherapy delivery to neoplasms relies on simple diffusion gradients from the intravascular to the interstitial space. Summarizes numerous barriers which prevent efficient iv. chemotherapy delivery to the target tumor cell.



The relative advantage (RT) of HAI over the typical intravenous route is given by the following formula:

$$RT = 1 + \frac{TBC}{Q(1-e)} \qquad \text{(Equation 1)}$$

(ΔP) and the oncotic pressure gradient across the capillary ($\Delta\prod$)" [7,8,63]. Starling's equation is as follows:

$$J_v = K_f((P_c - P_t) - \sigma(\Pi_c - \Pi_t)) \qquad \text{(Equation 2)}$$

Even IV systemic therapies reach tumors through IA route

Strategies for better delivery of chemotherapy

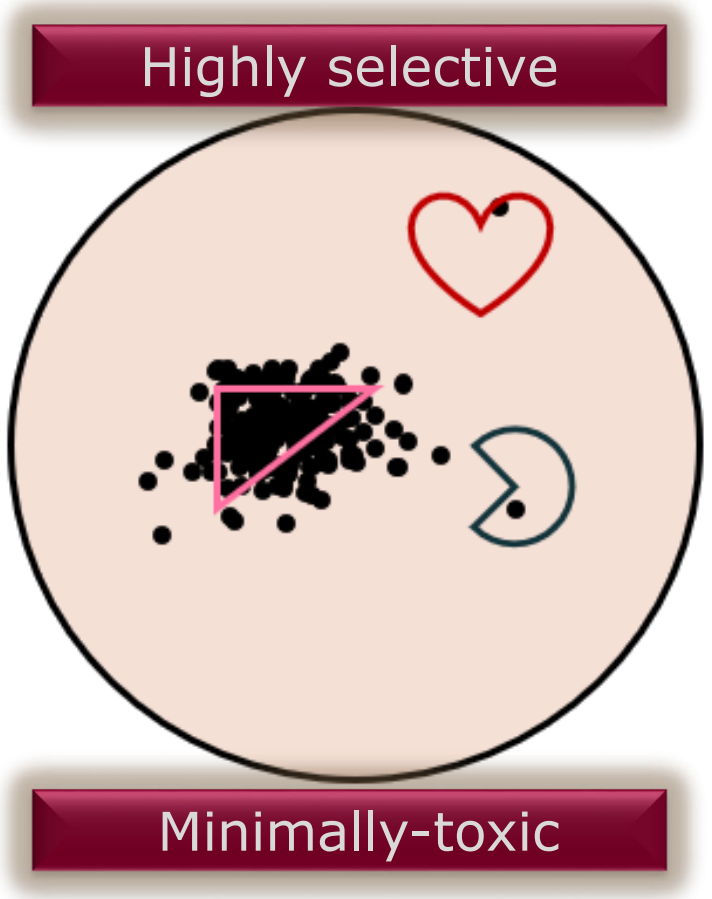
High local extraction and concentration

- Increase IV chemo dose
- Intra-arterial delivery close to tumor
- Increase permeability of drug
- Overcome blood-brain-barrier/ Blood-tumor-barrier
- Use of carrier molecules/vehicle
- Increase diffusion pressure

Short plasma half-life to avoid systemic accumulation

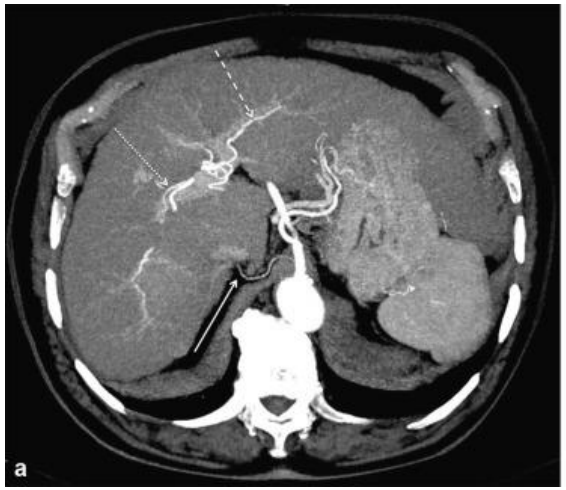
High total body clearance.

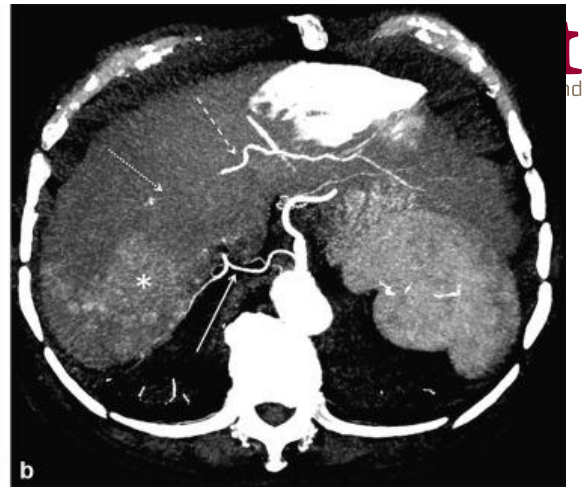
Intra-arterial delivery- Major treatment goals

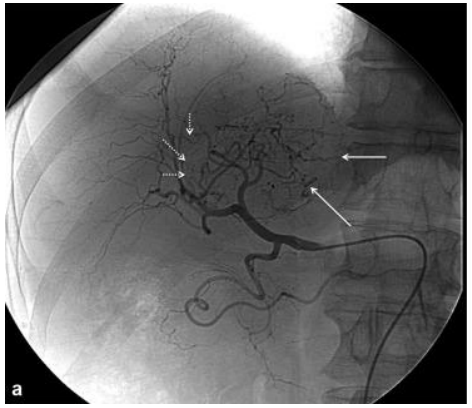


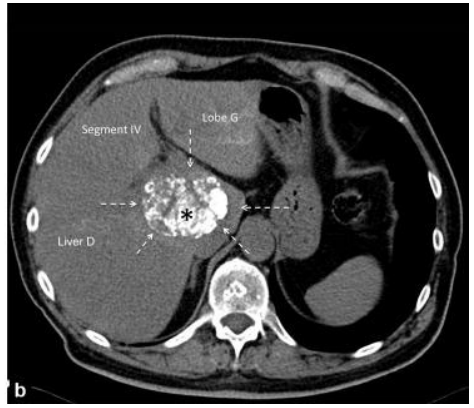
Siemann DW, Horsman MR. Vascular targeted therapies in oncology. Cell Tissue Res. 2009 Jan;335(1):241-8. doi: 10.1007/s00441-008-0646-0. Epub 2008 Aug 28. PMID: 18752004; PMCID: PMC2788502.

Anatomical variations & Aberrant Supply

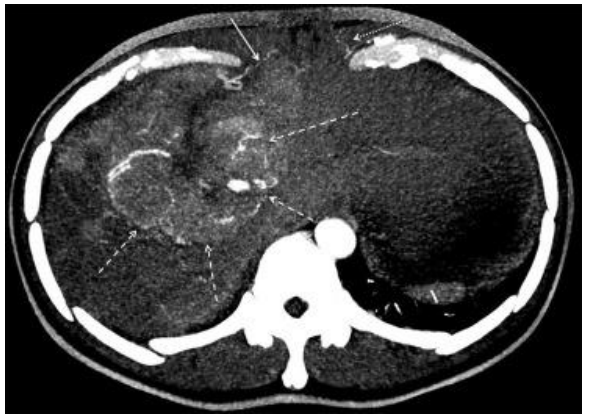


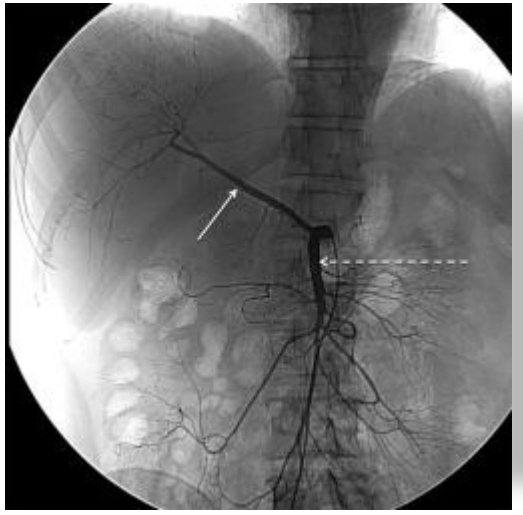


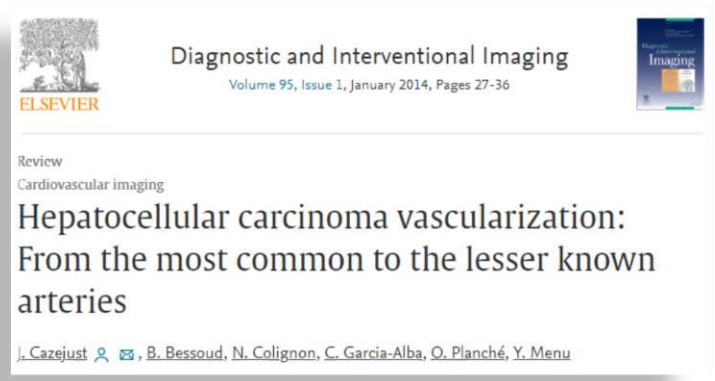




Technique







ELSEVIER

Diagnostic and Interventional Imaging

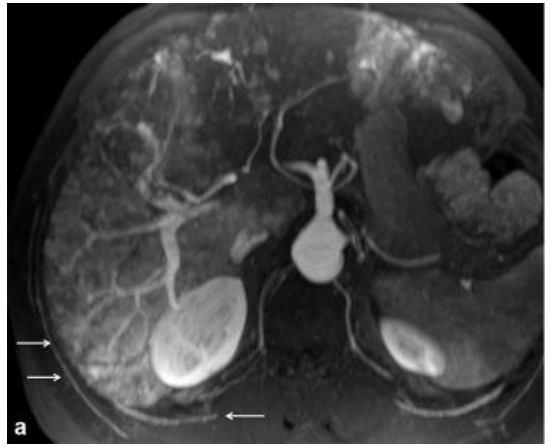
Volume 95, Issue 1, January 2014, Pages 27-36

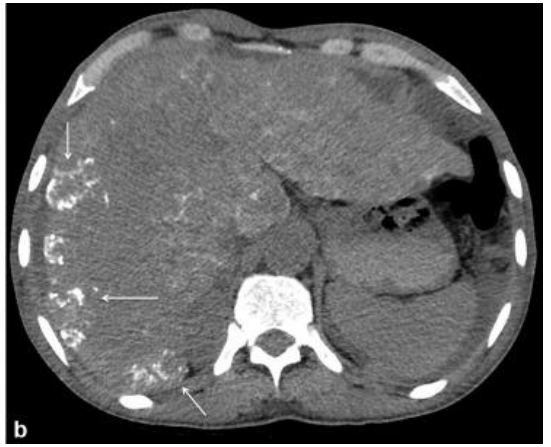
Review

Cardiovascular imaging

Hepatocellular carcinoma vascularization: From the most common to the lesser known arteries

J. Cazejust, B. Bessoud, N. Colignon, C. Garcia-Alba, O. Planché, Y. Menu





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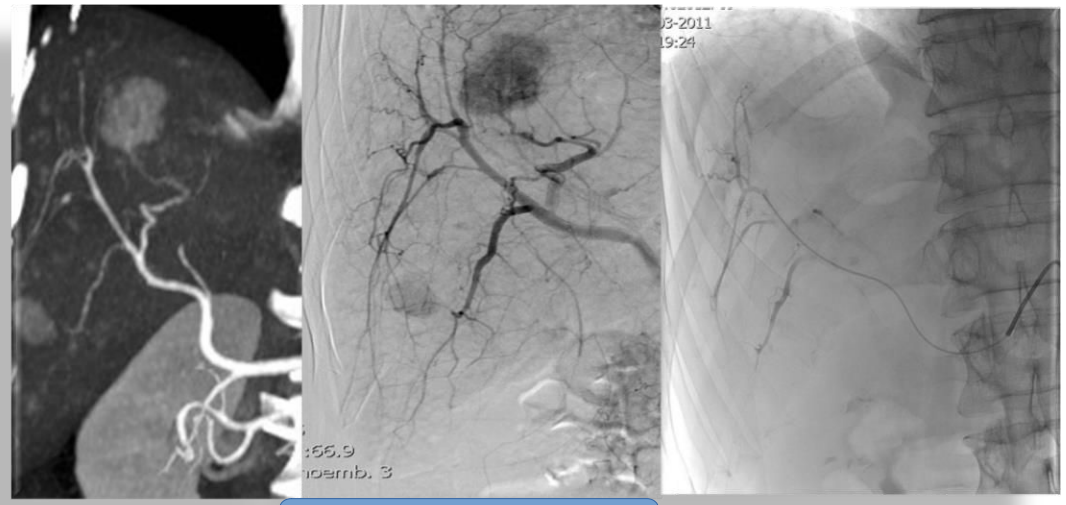
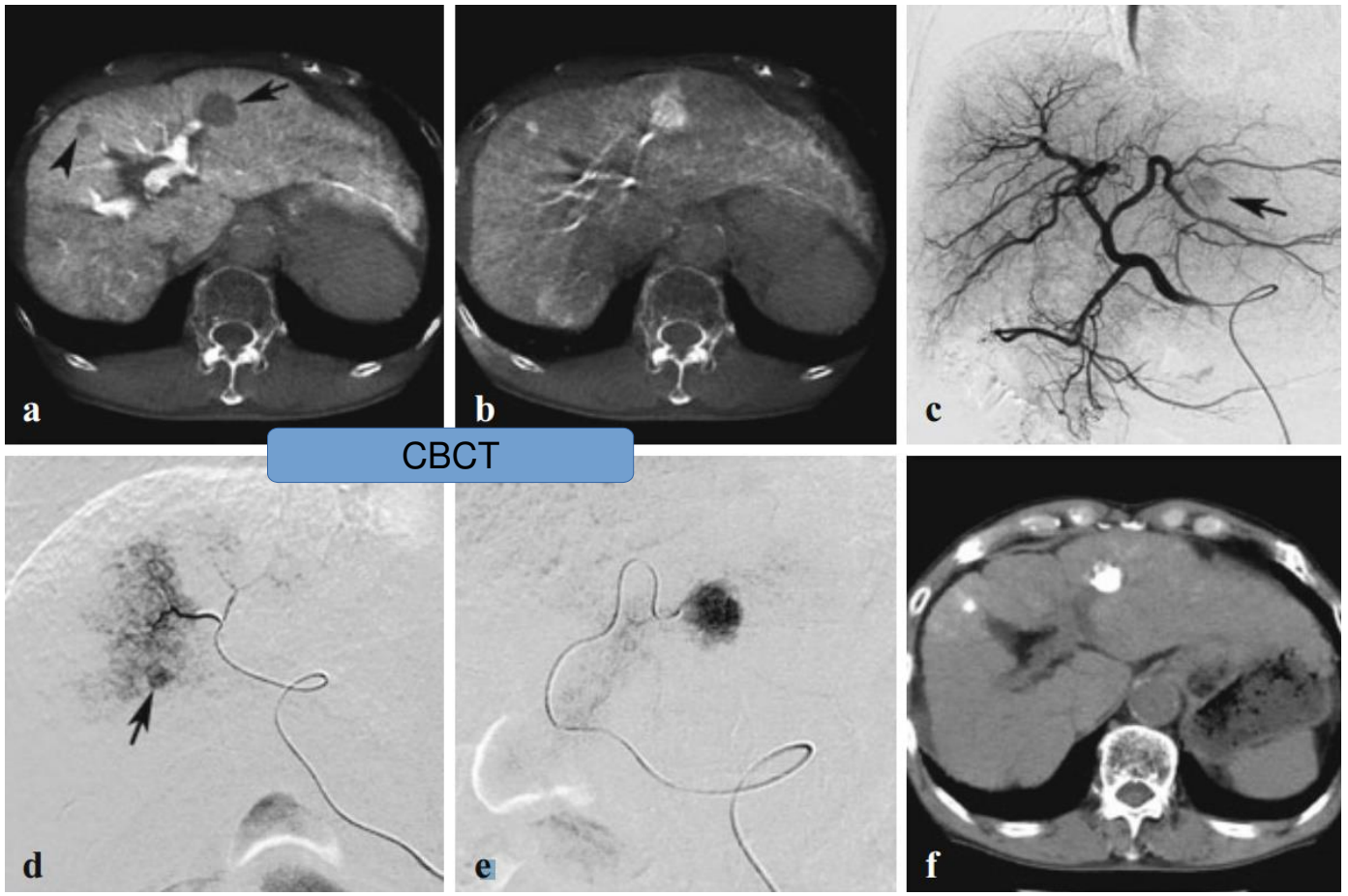


MIP assisted DSA



CBCT

ESSENTIAL PRE-REQUISITE for Successful intra-arterial therapy

Correct placement of catheter and

Optimal drug/particle delivery

Review > Jpn J Radiol. 2011 Jul;29(6):371-7. doi: 10.1007/s11604-011-0568-8. Epub 2011 Jul 24.

Efficacy of cone-beam computed tomography during transcatheter arterial chemoembolization for hepatocellular carcinoma

Shiro Miyayama [1], Masashi Yamashiro, Yuki Hattori, Nobuaki Orito, Ken Matsui, Kazunobu Tsuji, Miki Yoshida, Osamu Matsui

Does Intra-arterial Chemotherapy achieve required concentration ?

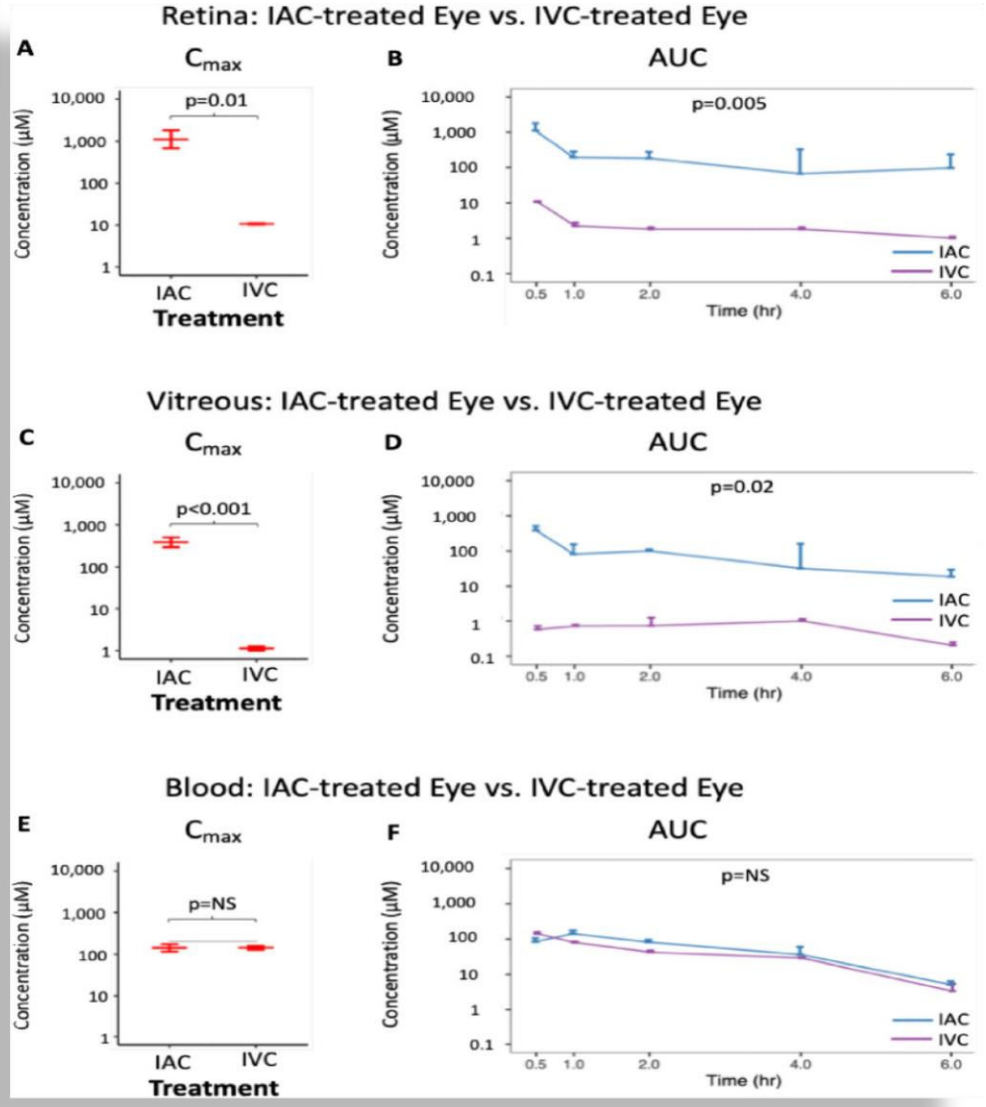
HCC/Liver mets

HAI

- Floxuridine (FUDR - 5-FU) short half-life
- Hepatic extraction rate ~ 95%,
- Tumor exposure ~ 400 times greater than the systemic infusion

Retinoblastoma

Intra-arterial chemo



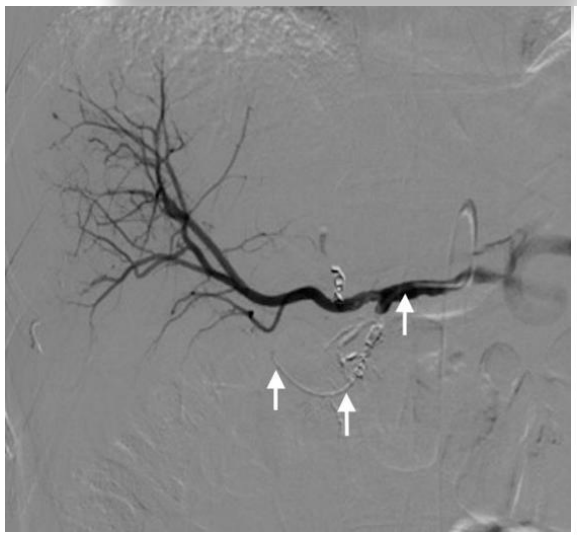
Laface C, Laforgia M, Molinari P, Ugenti I, Gadaleta CD, Porta C, Ranieri G. Hepatic Arterial Infusion of Chemotherapy for Advanced Hepatobiliary Cancers: State of the Art. Cancers (Basel). 2021 Jun 21;13(12):3091. doi: 10.3390/cancers13123091. PMID: 34205656; PMCID: PMC8234226.

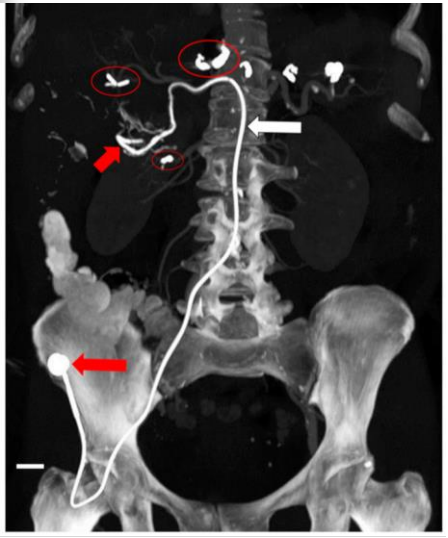
Daniels AB, Froehler MT, Kaczmarek JV, Bogan CM, Santapuram PR, Pierce JM, Chen SC, Schremp EA, Boyd KL, Tao YK, Calcutt MW, Koyama T, Richmond A, Friedman DL. Efficacy, Toxicity, and Pharmacokinetics of Intra-Arterial Chemotherapy Versus Intravenous Chemotherapy for Retinoblastoma in Animal Models and Patients. Transl Vis Sci Technol. 2021 Sep 1;10(11):10. doi: 10.1167/tvst.10.11.10. PMID: 34495330; PMCID: PMC8431978.

Majority of vascular cancer therapies are **ANTITUMOR AGENTS**

Chemotherapy

IAC Retinoblastoma
HAI





Chemotherapy + Particle Embolization

- HCC
- Liver Mets
- Lung
- Renal
- Retroperitoneum
- Bony Mets
- Gastric

Radiotherapy + Particles

SIRT/TARE – Liver

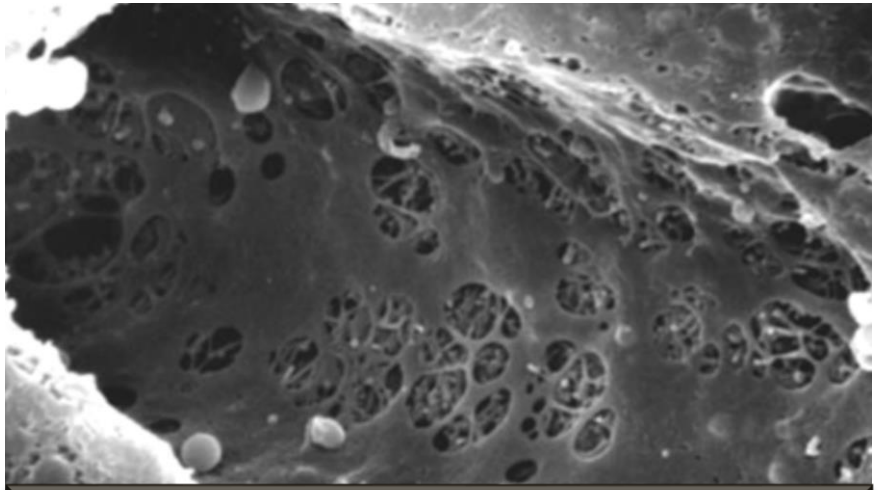
- Iodine 131
- Yttrium 90
- Rhenium 188
- Holmium 166
- Iodine 125

Chevallier O, Mvouama S, Pellegrinelli J, Guillen K, Manfredi S, Ghiringhelli F, Falvo N, Midulla M, Loffroy R. Percutaneous Implantation of a Microcatheter-Port System for Hepatic Arterial Infusion Chemotherapy of Unresectable Liver Tumors: Technical Feasibility, Functionality, and Complications. Diagnostics (Basel). 2021 Feb 26;11(3):399. doi: 10.3390/diagnostics11030399. PMID: 33652814; PMCID: PMC7996956.

Laface C, Laforgia M, Molinari P, Ugenti I, Gadaleta CD, Porta C, Ranieri G. Hepatic Arterial Infusion of Chemotherapy for Advanced Hepatobiliary Cancers: State of the Art. Cancers (Basel). 2021 Jun 21;13(12):3091. doi: 10.3390/cancers13123091. PMID: 34205656; PMCID: PMC8234226.

Neugut AI, Prigerson HG. Curative, Life-Extending, and Palliative Chemotherapy: New Outcomes Need New Names. Oncologist. 2017 Aug;22(8):883-885. doi: 10.1634/theoncologist.2017-0041. Epub 2017 May 26. PMID: 28550031; PMCID: PMC5553954.

Rationale for TACE & TARE/SIRT



LIVER

Terminal arterioles ~10-50

Met arterioles 10-20

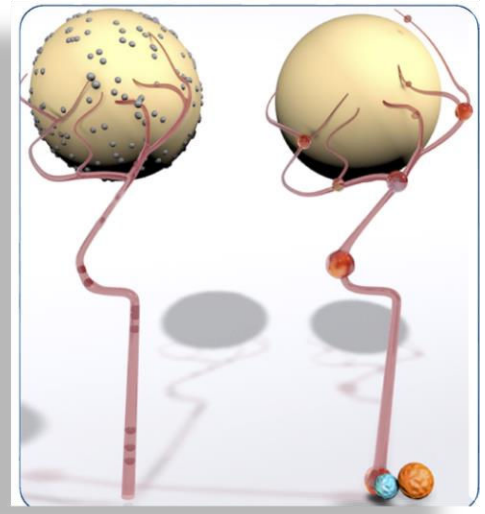
Capillary 8-30

Collecting venules 10-50

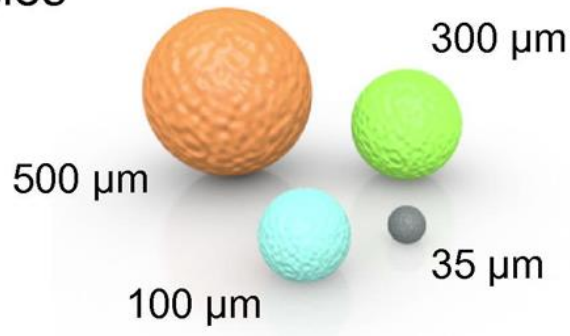
DSMs 50 ± 7µm microspheres
DEB-TACE 300–500 µm

Lipiodol small 10–40-µm and large 30–120-µm droplet W/O and O/W

Therasphere (20-30 µm)	SIR-sphere (20-60 µm)
90Y Mixed with glass matrix	Surface of resin sphere
Activity per sphere 2,500 Bq*	50 Gq



Particles

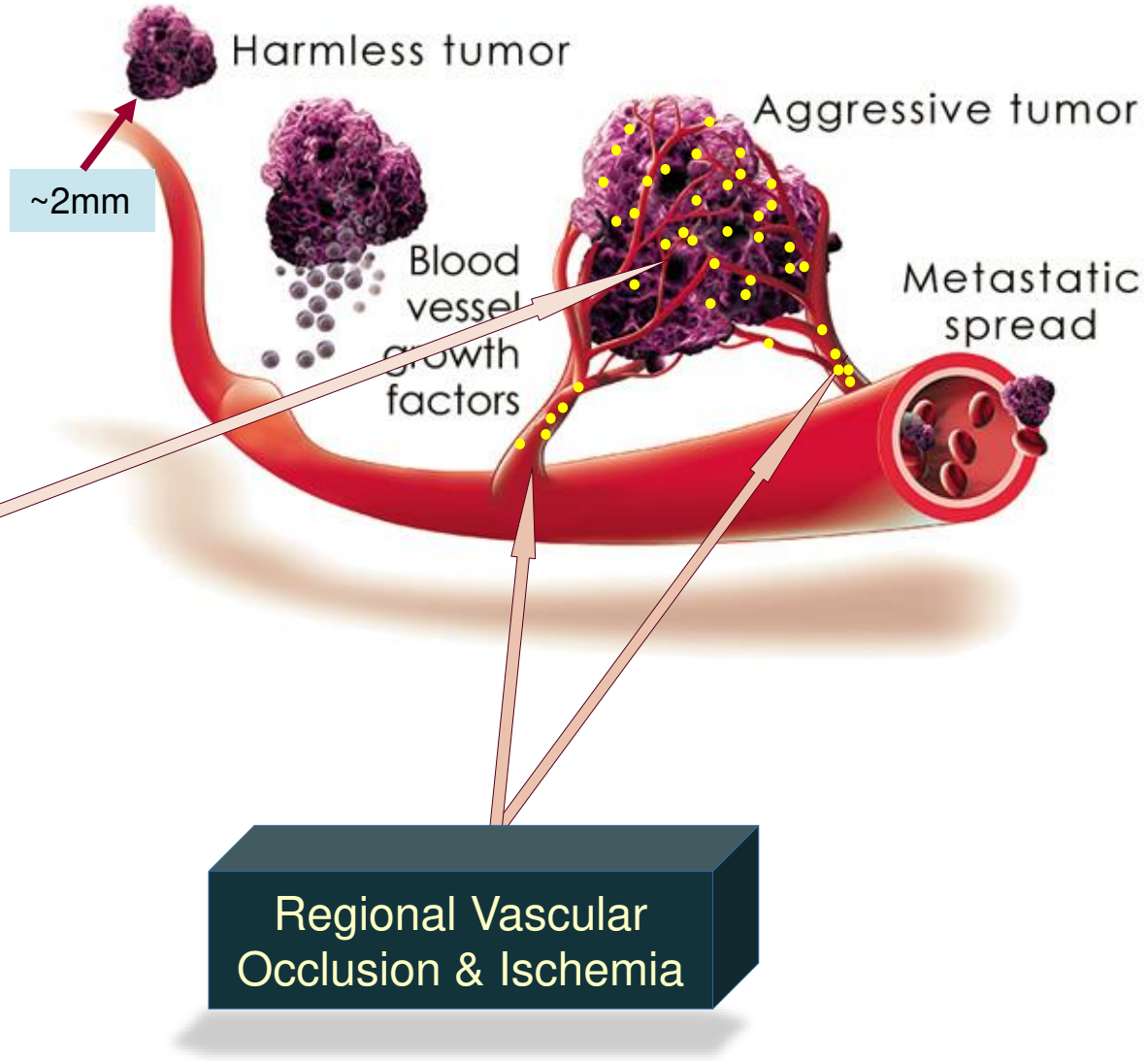


Large enough not to pass through capillaries

Small enough to lodge in the tumor vascular bed

https://www.science.org/doi/10.1126/sciadv.abb0020

Rationale for DEB-TACE & TARE/SIRT



Local Antitumor activity

Regional Vascular Occlusion & Ischemia

Zuazo-Gaztelu I, Casanovas O. Unraveling the Role of Angiogenesis in Cancer Ecosystems. Front Oncol. 2018 Jul 2;8:248. doi: 10.3389/fonc.2018.00248. PMID: 30013950; PMCID: PMC6036108.

https://www.science.org/doi/10.1126/sciadv.abb0020

https://evtoday.com/articles/2018-apr/ctace-the-rebirth-of-lipiodol

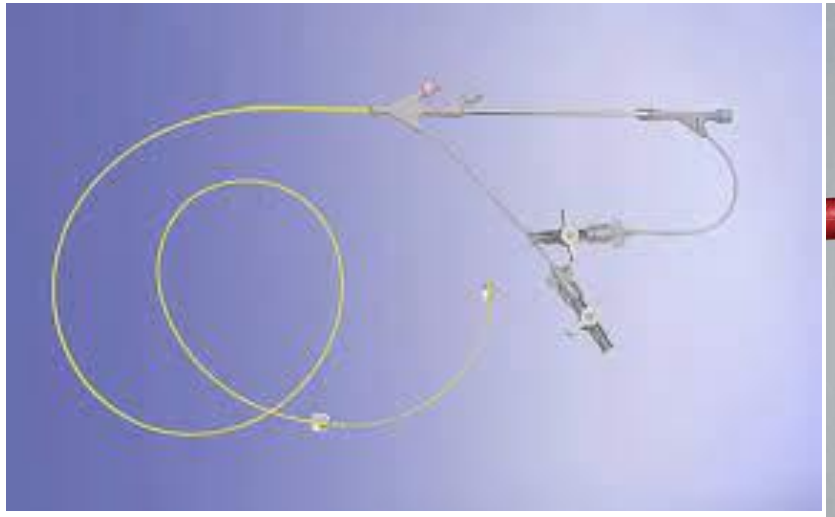
Yildiz I, Deniz S, Ozer A, Caliskan K. Trans-Arterial Chemoembolization with 50 µm Degradable Starch Microspheres Versus 300–500 µm Drug Eluting Beads in Hepatocellular Carcinoma: A Comparative Analysis of Initial Treatment Outcomes. Journal of the Belgian Society of Radiology. 2022;106(1):10. DOI: http://doi.org/10.5334/jbsr.2594

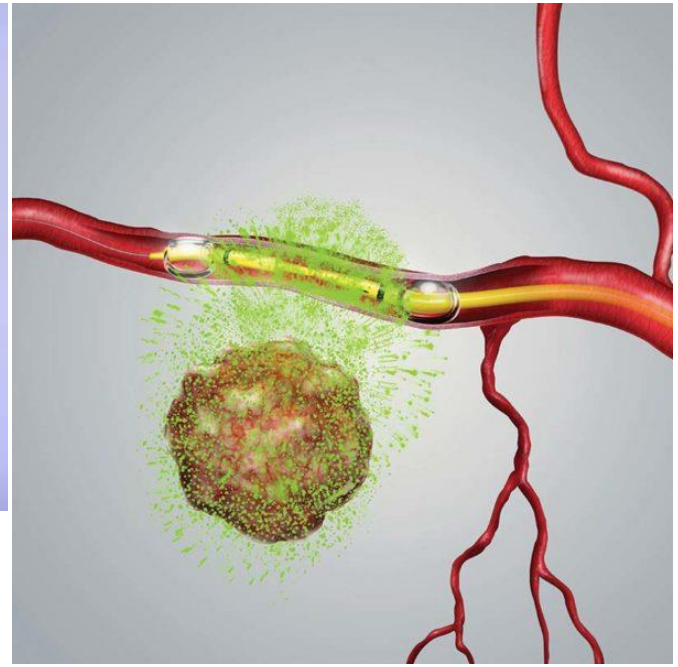
Jin Woo Choi, Hyo-Cheol Kim. Radioembolization for hepatocellular carcinoma: what clinicians need to know. J Liver Cancer 2022;22(1):4-13 pISSN 2288-8128 • eISSN 2383-5001 https://doi.org/10.17998/jlc.2022.01.16

Trans-Arterial Chemotherapy for Treatment of Locally Advanced Pancreatic Cancer: Treatment Factors Impacting Survival

H. Charles Li – RenovoRx

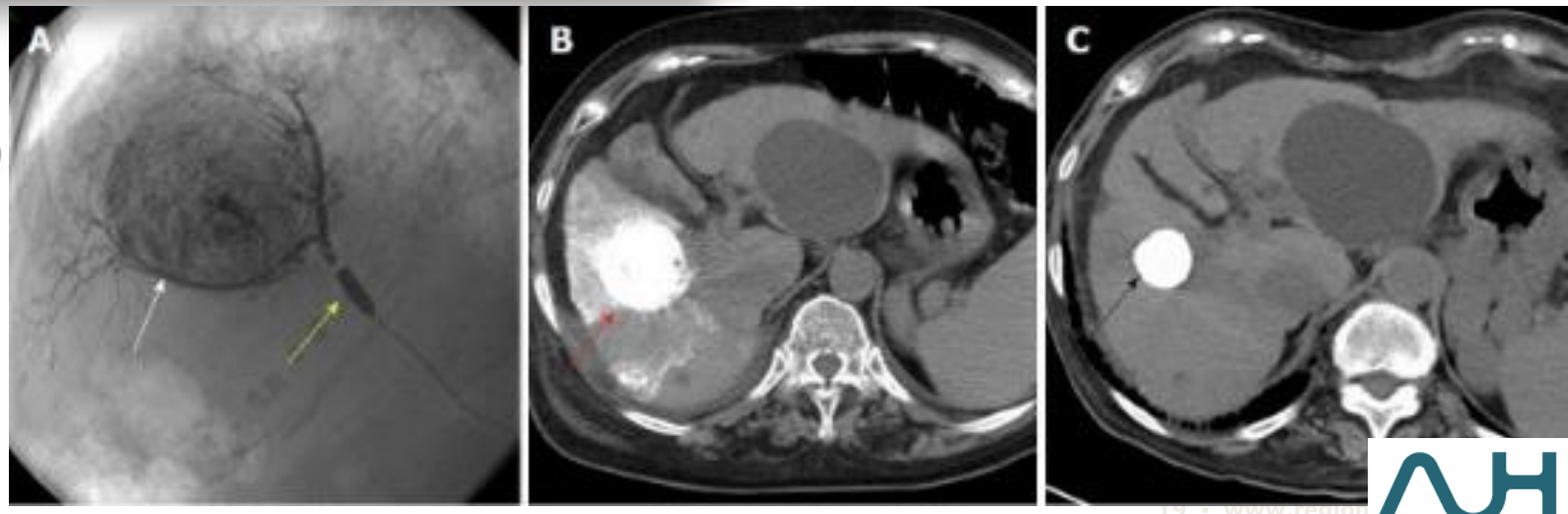
Alex S. Tsobanoudis, Jiali Li, Alexander Rosemurgy, J. Augusto Bastidas, Emmanuel Zervos, Steven Goldin, Peter Muscarella II, Charles Nutting, Barish Edil, Reza Malek, Ramtin Agah





How to Improve drug delivery ??

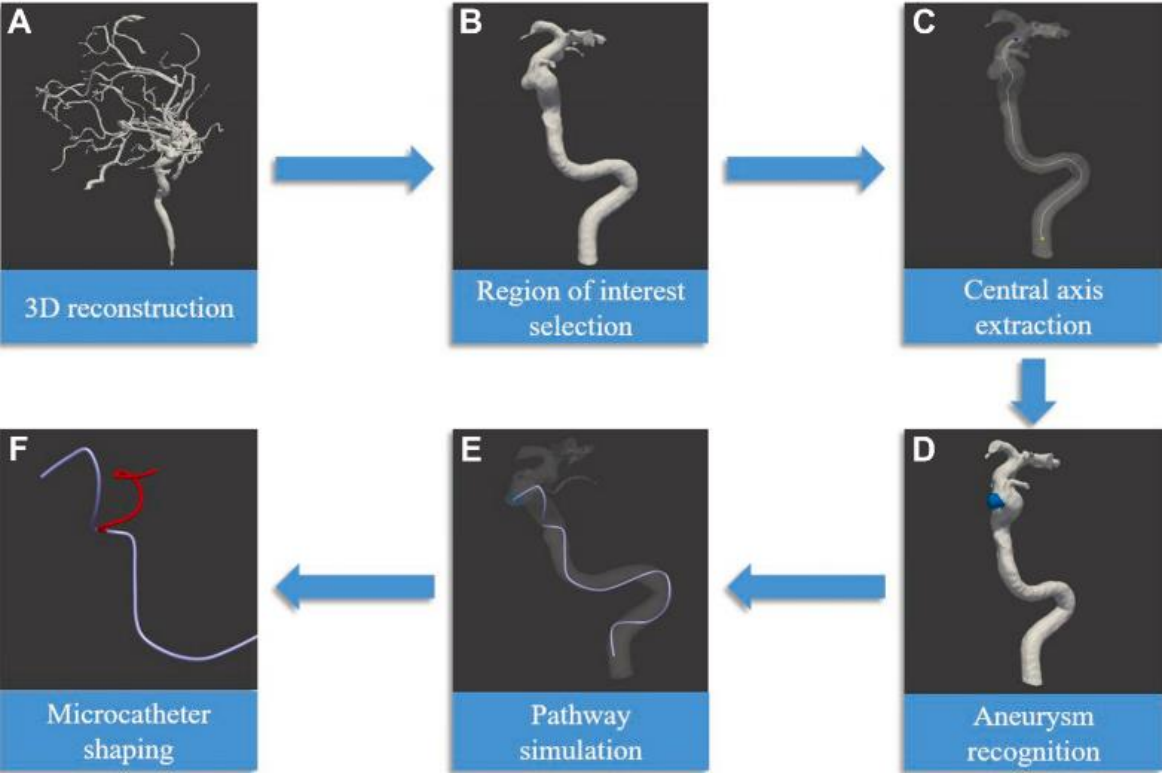
Increase diffusion pressure



World J Hepatol. Jul 27, 2018; 10(7): 485-495
Published online Jul 27, 2018. doi: 10.4254/wjh.v10.i7.485

Balloon-occluded transcatheter arterial chemoembolization for hepatocellular carcinoma

Takeshi Hatanaka, Hirotaka Arai, Satoru Kakizaki

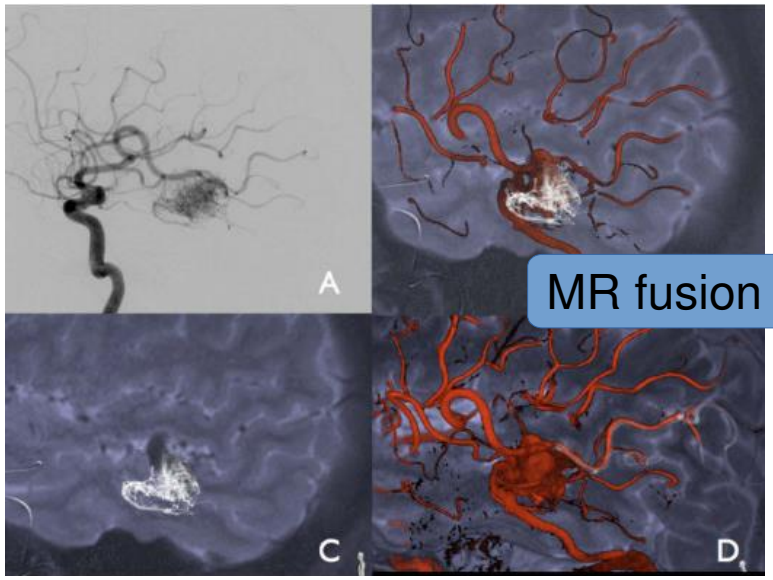


FULL TEXT ARTICLE

Artificial Intelligence-Assisted Microcatheter Shaping for Intracranial Aneurysm Coiling: A Preliminary Study

Changya Liu, Yin Shen, Xinxin Wu, Kang Qian, Xuebin Hu and Haifeng Yang

Annals of Vascular Surgery, 2022-09-01, Volume 85, Pages 228-236, Copyright © 2022 Elsevier Inc.



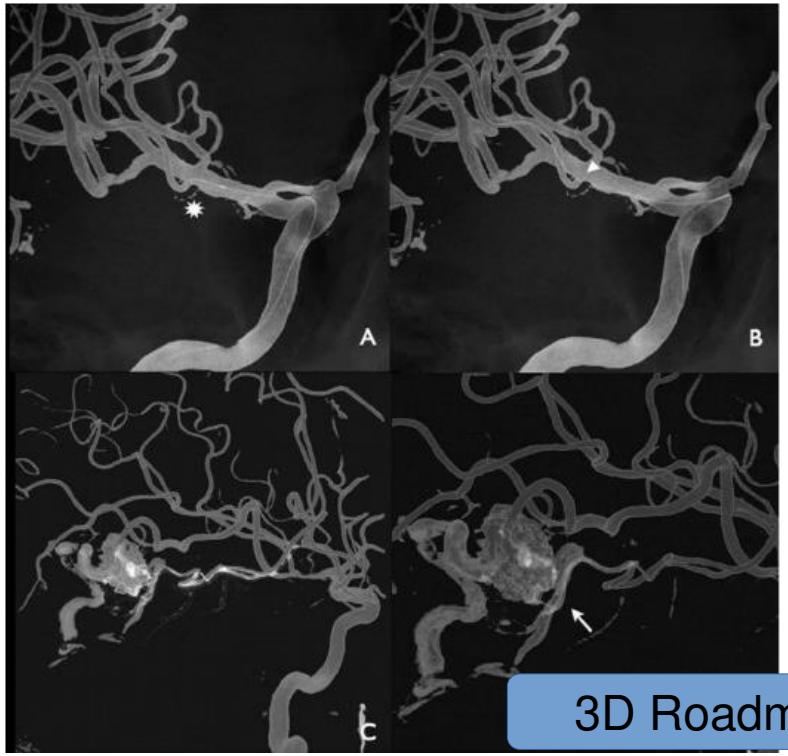
MR fusion with DSA

Neuroimaging

ORIGINAL RESEARCH

Multimodal angiographic assessment of cerebral arteriovenous malformations: a pilot study

Raphaël Blanc,[1] Aude Seiler,[1] Thomas Robert,[1] Humain Baharvahdat,[2] Maxime Lafarge,[1,3] Julien Savatovsky,[4] Jérôme Hodel,[5] Gabriele Ciccio,[1] Dorian Chauvet,[6] Silvia Pistocchi,[1] Bruno Bartolini,[1] Hocine Redjem,[1] Michel Piotin[1]



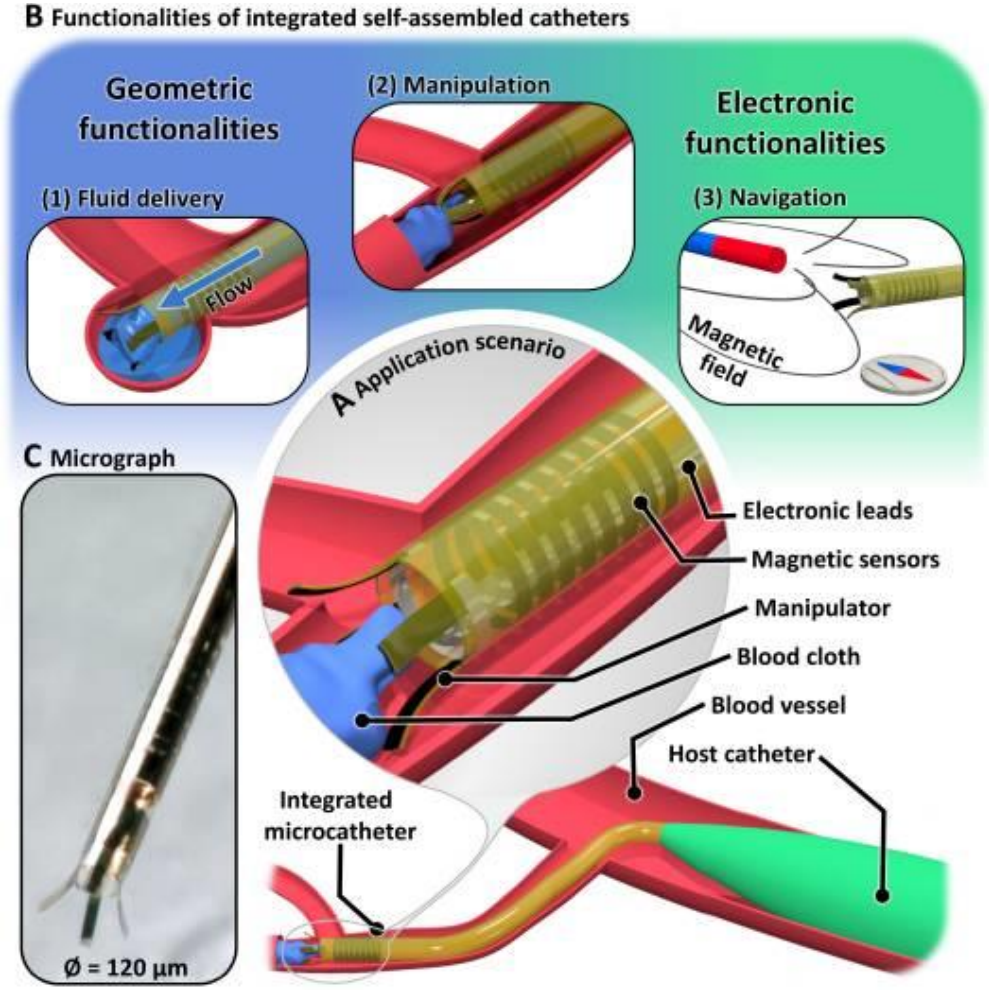
3D Roadmap

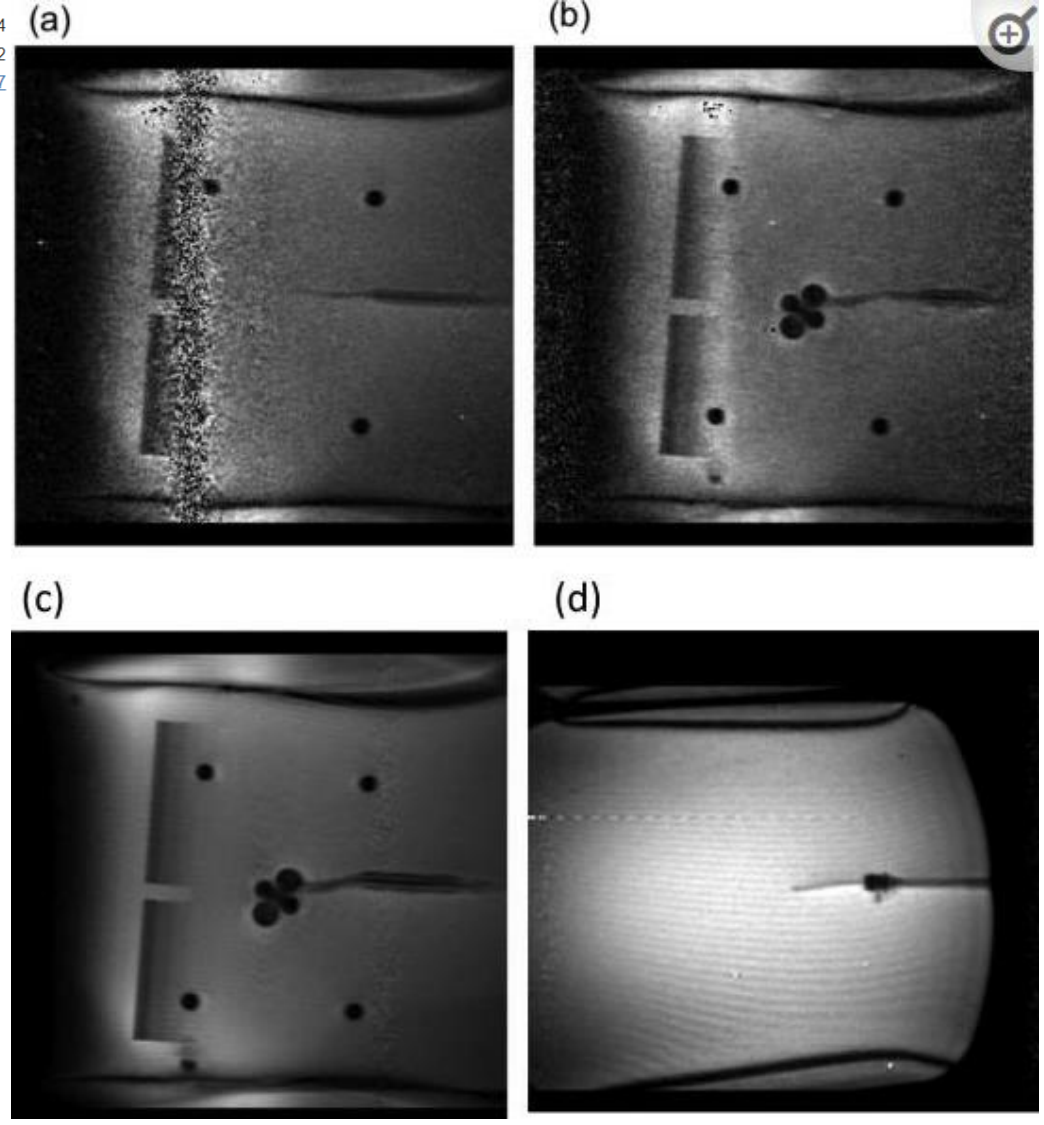
Biomed Microdevices. Author manuscript; available in PMC 2015 Feb 1.
Published in final edited form as:
Biomed Microdevices. 2014 Feb; 16(1): 97–106.
doi: 10.1007/s10544-013-9809-1

PMCID: PMC3945604
NIHMSID: NIHMS532482
PMID: 24132857

System architecture for a magnetically guided endovascular microcatheter

Ryan S. Sincic, R.S.S,[1] Curtis J. Caton, C.J.C.,[2] Prasheel Lillaney, P.L.,[1] Scott Goodfriend, S.G.,[2] Jason Niemi, J.N.,[2] Alastair J. Martin, A.J.M.,[1] Aaron D. Losey, A.D.L.,[1] Neel Shah, N.S.,[1] Erin J. Yee, E.J.Y.,[1] Lee Evans, L.E.,[1] Vincent Malba, V.M.,[1] Anthony F. Bernhardt, A.F.B.,[1] Fabio Settecase, F.S.,[1] Daniel L. Cooke, D.L.C.,[1] Maythem Saeed, M.S.,[1] Mark W. Wilson, M.W.W.,[1] and Steven W. Hetts, S.W.H.[1]

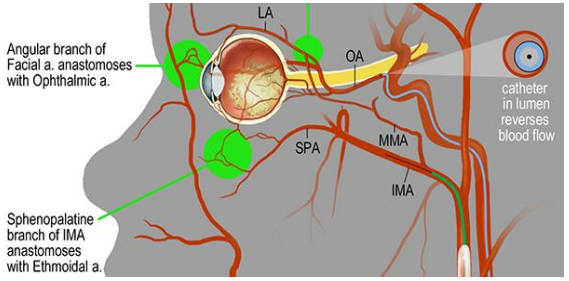




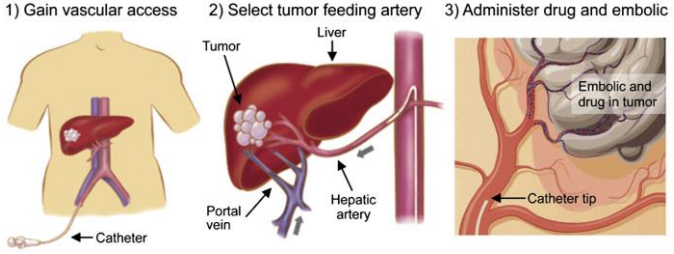
Rivkin B, Becker C, Singh B, Aziz A, Akbar F, Egunov A, Karnaushenko DD, Naumann R, Schäfer R, Medina-Sánchez M, Karnaushenko D, Schmidt OG. Electronically integrated microcatheters based on self-assembling polymer films. Sci Adv. 2021 Dec 17;7(51):eabl5408. doi: 10.1126/sciadv.abl5408. Epub 2021 Dec 17. PMID: 34919439; PMCID: PMC8682992.

Interventional Vascular Therapies for Cancer

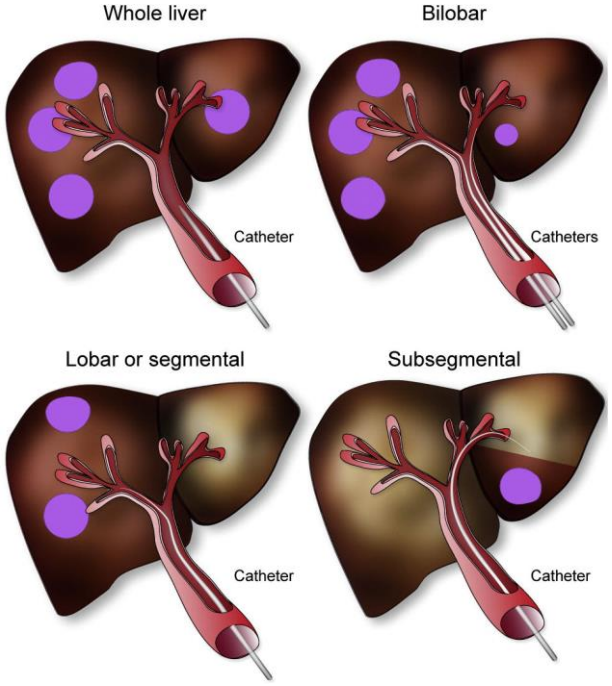
Intraarterial Chemotherapy Infusion



Chemotherapy with embolization (TACE)



Internal Radiotherapy



Endovascular RFA

Endovascular Brachytherapy

Future

Thermal therapy

Endovascular therapy-based light illumination technology (ET-BLIT)

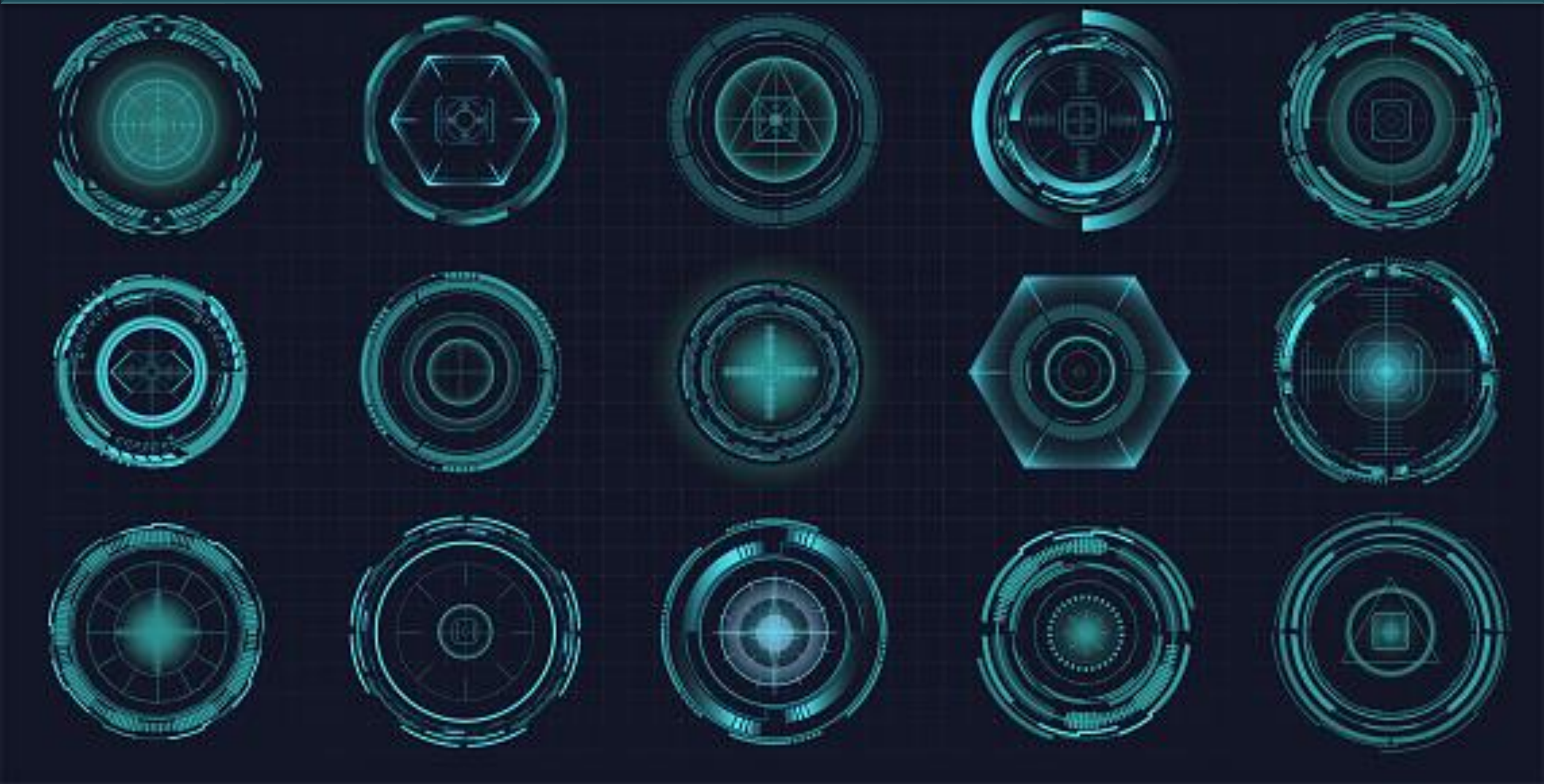
Nanovector targeted delivery

Andrew L. Lewis, Matthew R. Dreher. Locoregional drug delivery using image-guided intra-arterial drug eluting bead therapy. Journal of Controlled Release. Volume 161, Issue 2, 2012, Pages 338-350, ISSN 0168-3659. https://doi.org/10.1016/j.jconrel.2012.01.018.

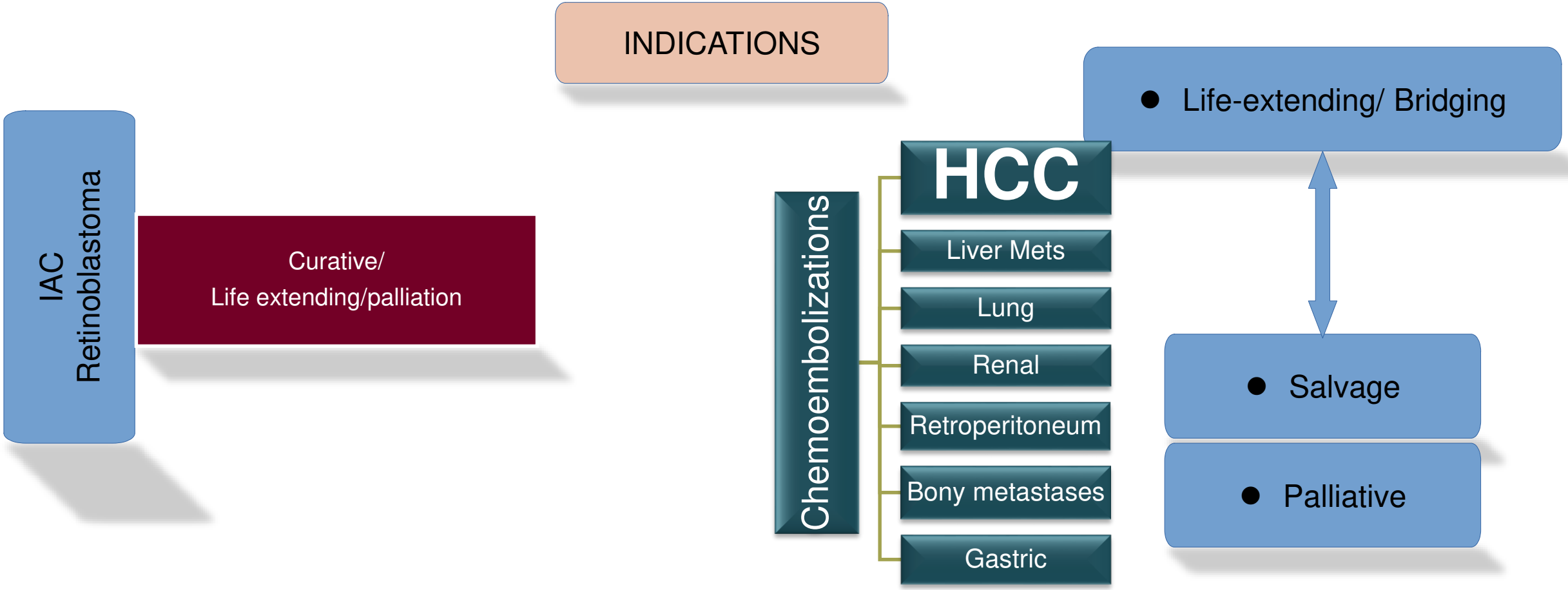
https://blog.cincinnatichildrens.org/radiology/finding-new-better-ways-treat-eye-cancer/

Bruno Sangro, Mercedes Iñarrairaegui, Jose I. Bilbao. Radioembolization for hepatocellular carcinoma. Journal of Hepatology 2012 (56-2); 464-473. ISSN 0168-8278, https://doi.org/10.1016/j.jhep.2011.07.012.

Goals and Indications

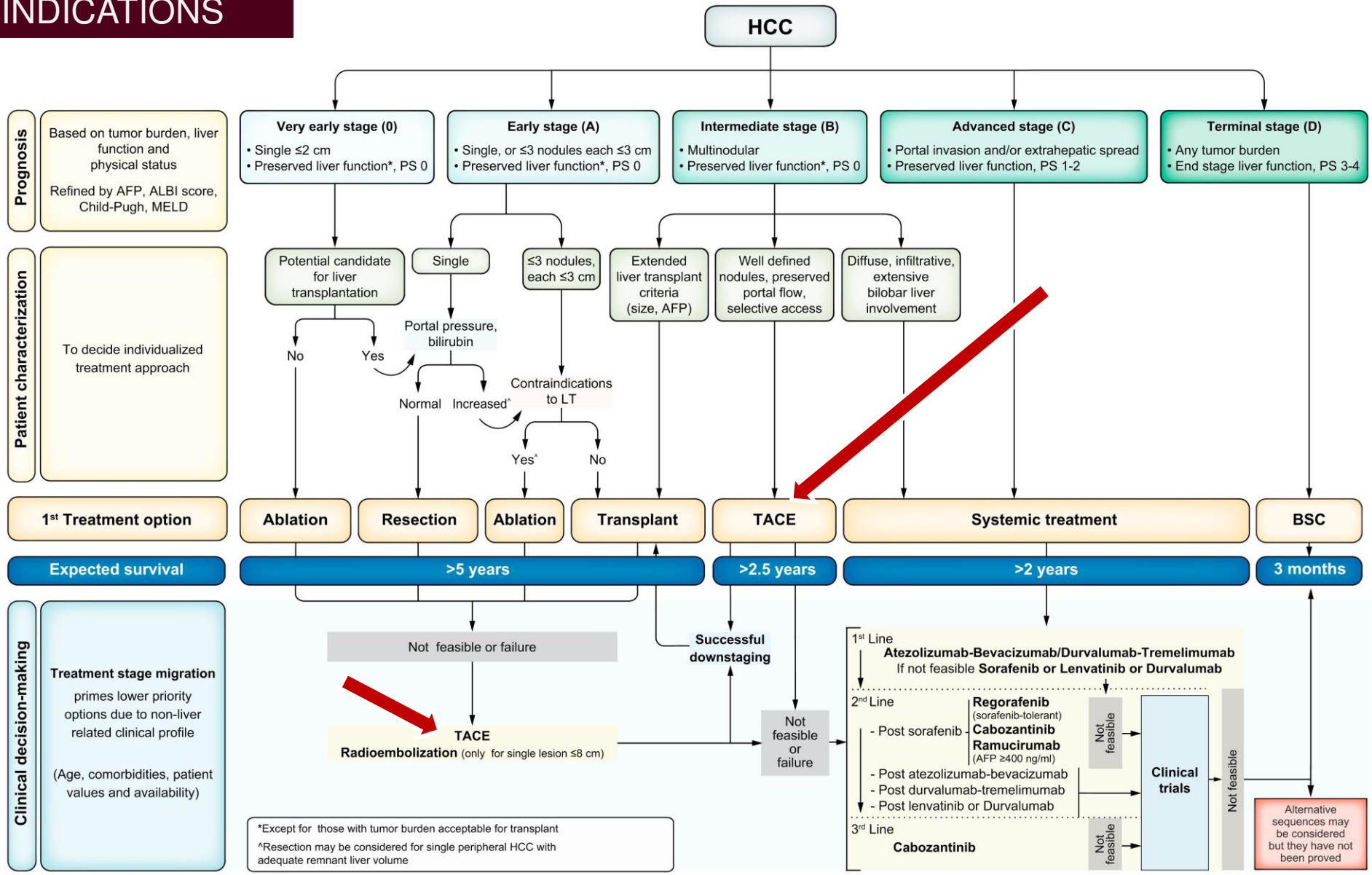


Goal of Intra-arterial vascular therapies



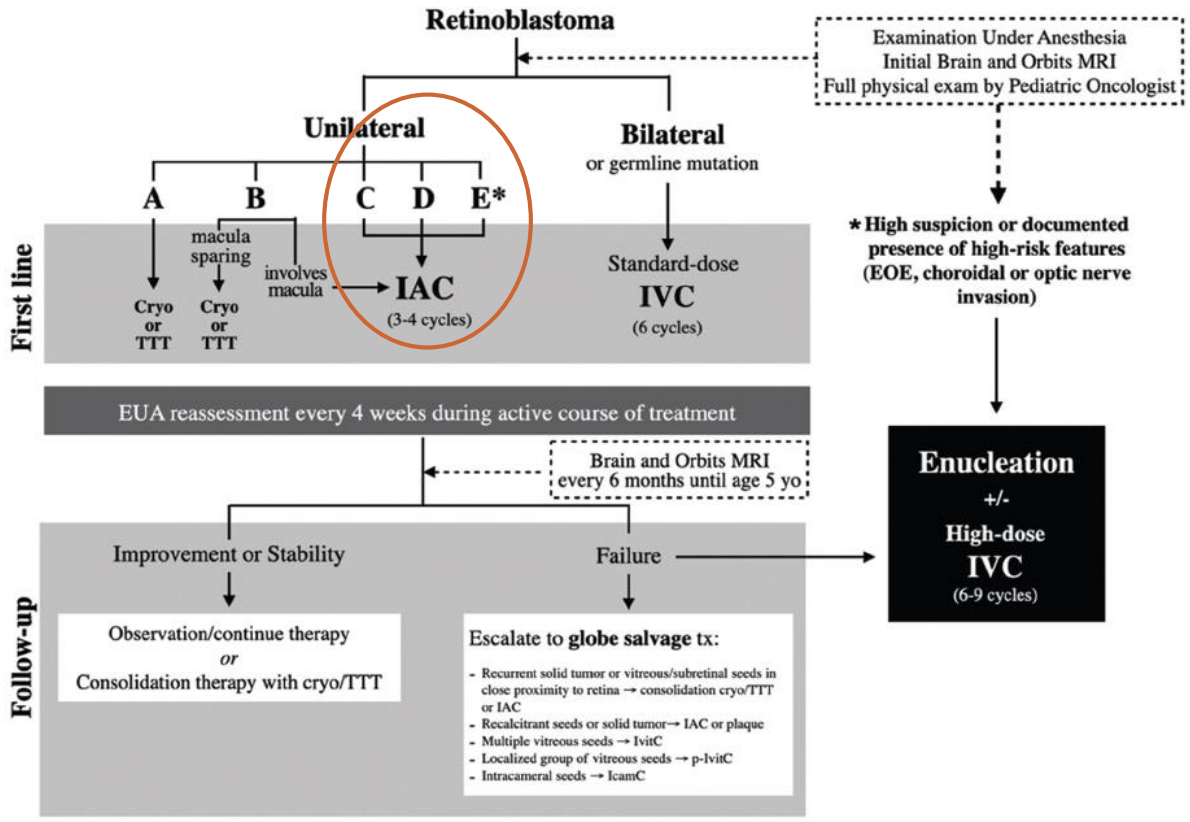
Neugut AI, Prigerson HG. Curative, Life-Extending, and Palliative Chemotherapy: New Outcomes Need New Names. Oncologist. 2017 Aug;22(8):883-885. doi: 10.1634/theoncologist.2017-0041. Epub 2017 May 26. PMID: 28550031; PMCID: PMC5553954.

HCC INDICATIONS



Reig M, Forner A, Rimola J, Ferrer-Fàbrega J, Burrel M, Garcia-Criado Á, Kelley RK, Galle PR, Mazzaferro V, Salem R, Sangro B, Singal AG, Vogel A, Fuster J, Ayuso C, Bruix J. BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update. J Hepatol. 2022 Mar;76(3):681-693. doi: 10.1016/j.jhep.2021.11.018. Epub 2021 Nov 19. PMID: 34801630; PMCID: PMC8866082.

Retinoblastoma – indications for IAC



Kenya National Retinoblastoma Strategy Best Practice Guidelines 2019

ANNEX 1

MANAGEMENT FOR RETINOBLASTOMA

All E eyes	Enucleate
Unilateral RB Group B-D	Enucleate
Bilateral RB Group A-D	Salvage
Group A	Focal Laser or Cryoptherapy
Group B-D	Chemoreduction + focal treatment
Pathology pT2a	No Chemotherapy
Pathology pT2b-PT3a	4 courses of chemotherapy
Pathology pT3b and worse	6 courses of Chemotherapy + Radiotherapy
Proptosis without metastasis	Chemotherapy before enucleation
Metastasis	Palliative chemotherapy/radiotherapy

Ancona-Lezama D, Dalvin LA, Shields CL. Modern treatment of retinoblastoma: A 2020 review. Indian J Ophthalmol. 2020 Nov;68(11):2356-2365. doi: 10.4103/ijo.IJO_721_20. PMID: 33120616; PMCID: PMC7774148.

Success / effectiveness Criteria

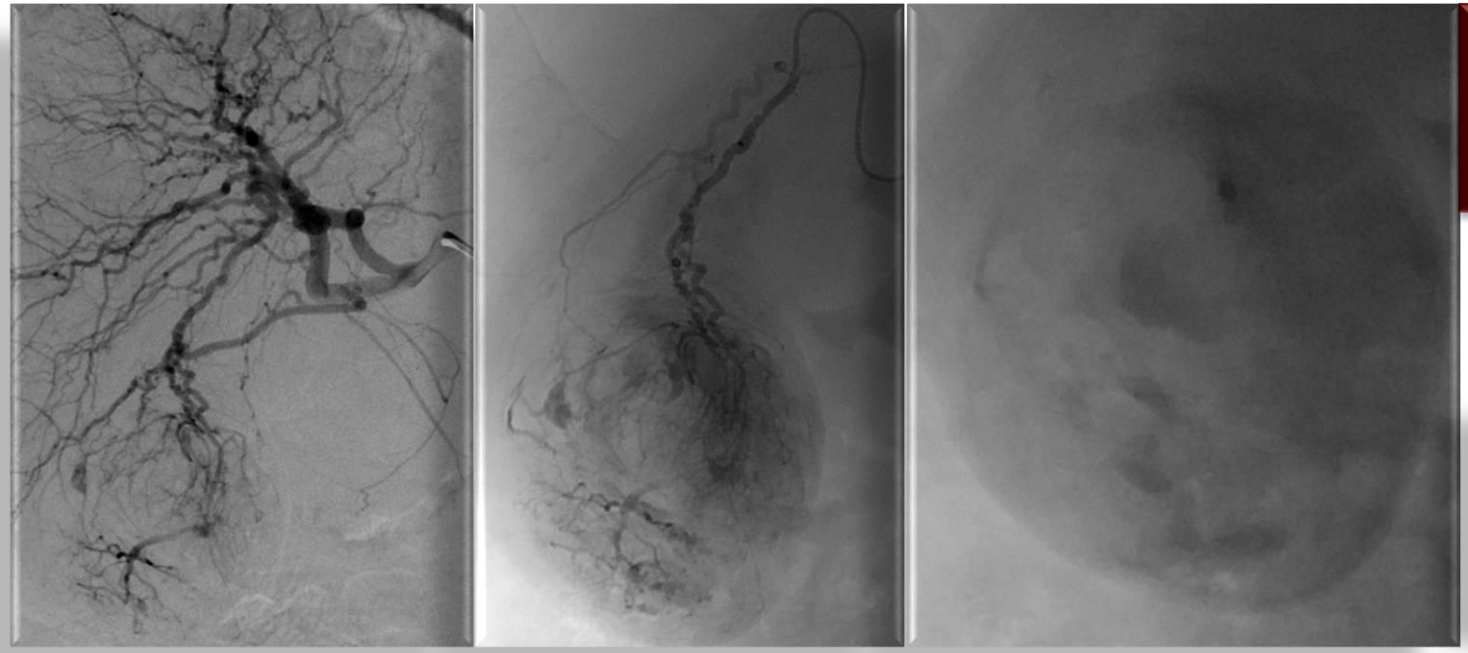
PROCEDURE TYPES OR SUBSETS
QI Definitions

- *Technical success* is defined as successful advancement of a catheter into a tumor vascular supply and transarterial therapy (selected chemotherapeutic and embolic agents) administration according to an investigator-designated plan (32).
- *Clinical success* is defined as technique effectiveness resulting in the desired clinical outcome (eg, effective palliation, bridging to transplantation, or tumor downstaging).
- *Technique effectiveness* is defined by response to treatment assessed at imaging follow-up at a prospectively defined time point (eg, 1–3 months after a treatment cycle) using standardized, validated radiologic response criteria (86–89).
- *Effective palliation* is defined by control or elimination of cancer-related symptoms (as in patients with symptomatic, hormone-secreting NETs) or by clinical outcome improvement quantified using standard oncologic measures such as OS, PFS, or TTP (as in tumors such as HCC and CLM).
- *Adverse events* are defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure (32).

STANDARDS OF PRACTICE

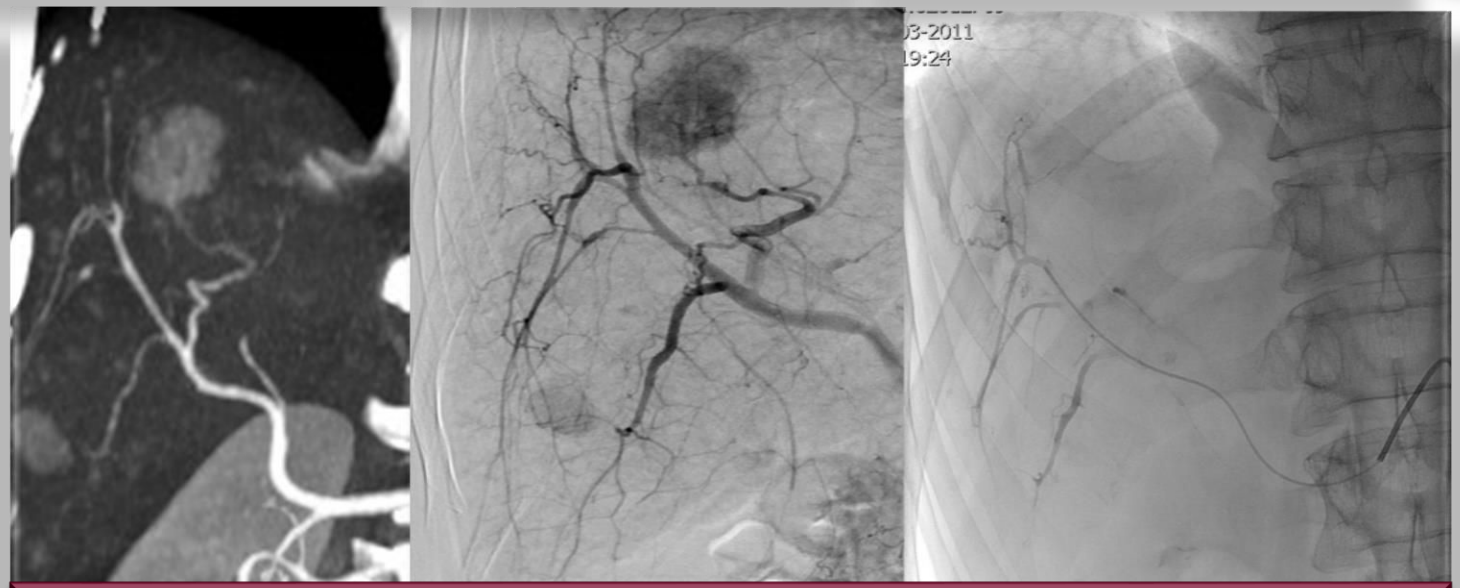
Quality Improvement Guidelines for Transarterial Chemoembolization and Embolization of Hepatic Malignancy

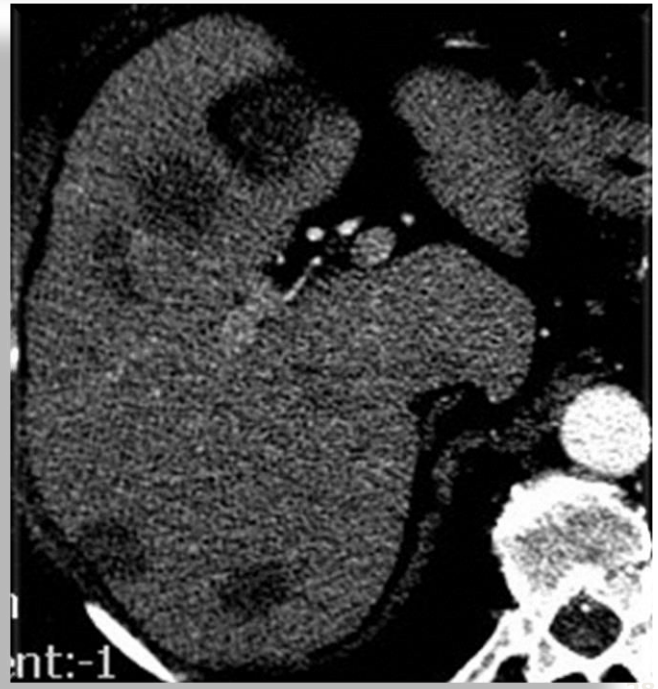
Ron C. Gaba, MD, R. Peter Lokken, MD, MPH, Ryan M. Hickey, MD, Andrew J. Lipnik, MD, Robert J. Lewandowski, MD, Riad Salem, MD, MBA, Daniel B. Brown, MD, T. Gregory Walker, MD, James E. Silberzweig, MD, Mark Otto Baerlocher, MD, Ana Maria Echenique, MD, Mehran Midia, MD, Jason W. Mitchell, MD, MPH, MBA, Siddharth A. Padia, MD, Suvranu Ganguli, MD, Thomas J. Ward, MD, Jeffrey L. Weinstein, MD, Boris Nikolic, MD, MBA, and Sean R. Dariushnia, MD, for the Society of Interventional Radiology Standards of Practice Committee



Technical success - Percutaneous placement of catheter in hepatic artery/branches followed by injection

TACE

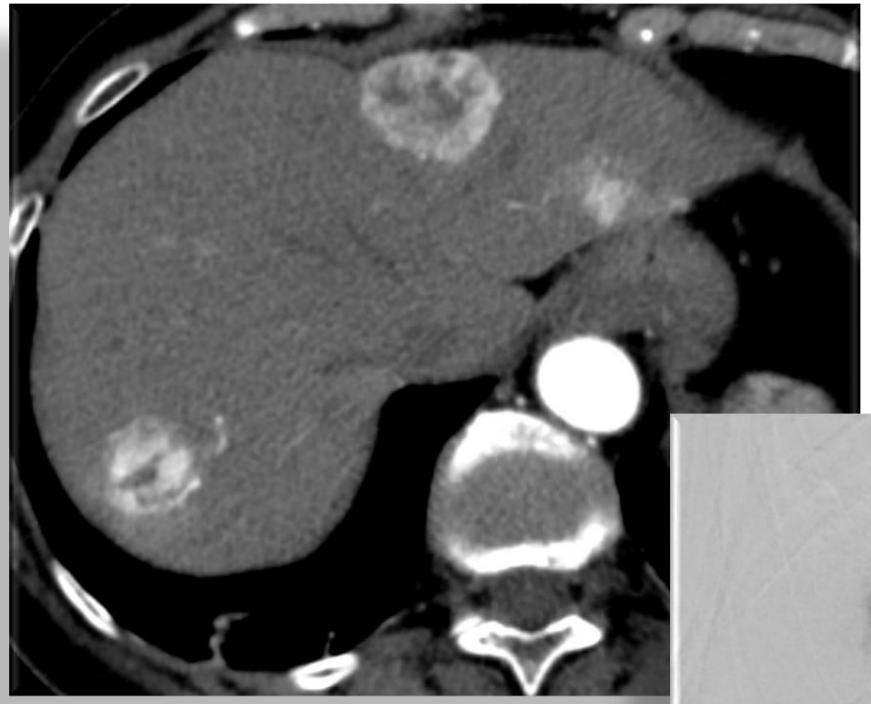


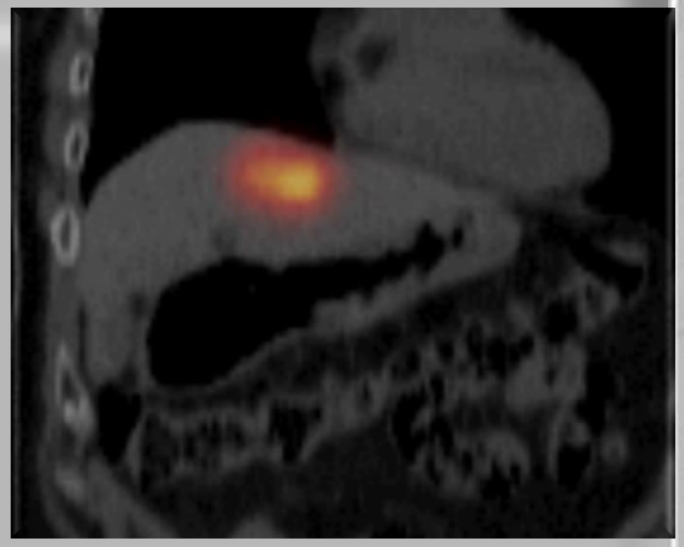


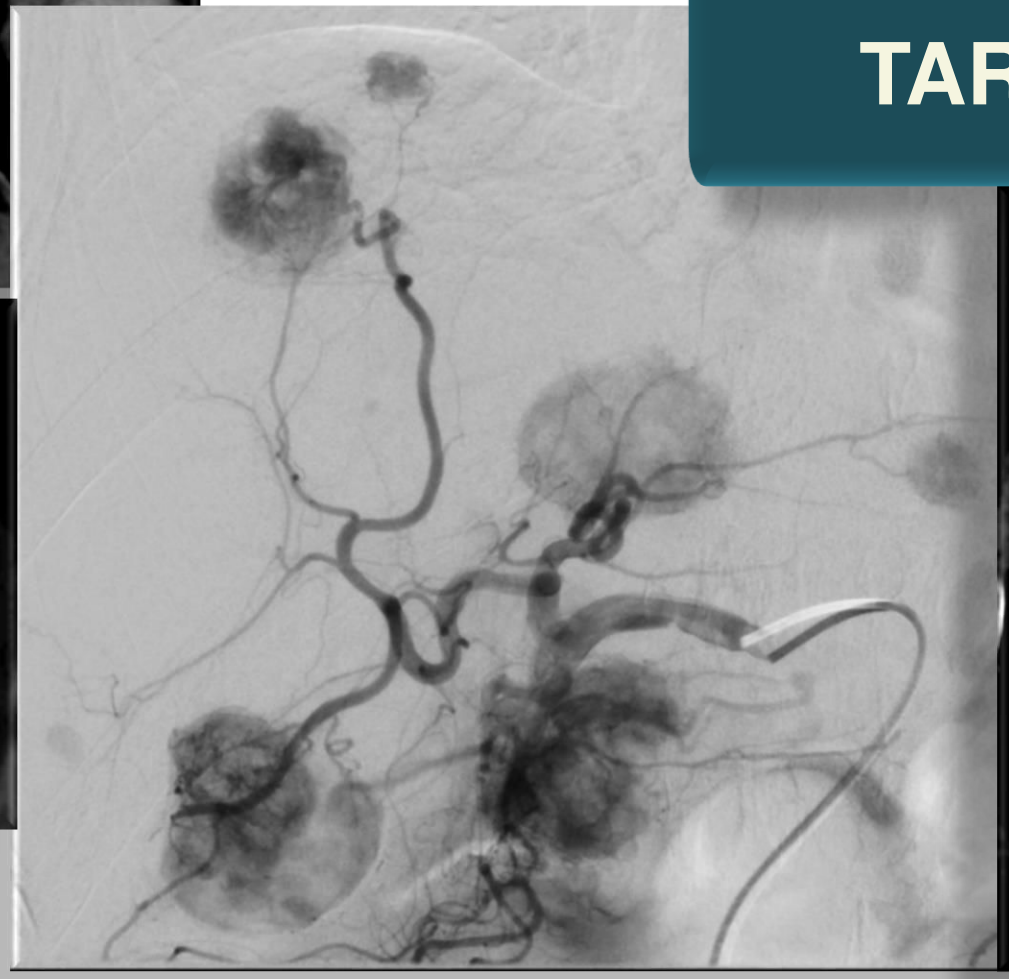
Technical effectiveness – Obtaining adequate Objective response by Imaging criteria (mRECIST)

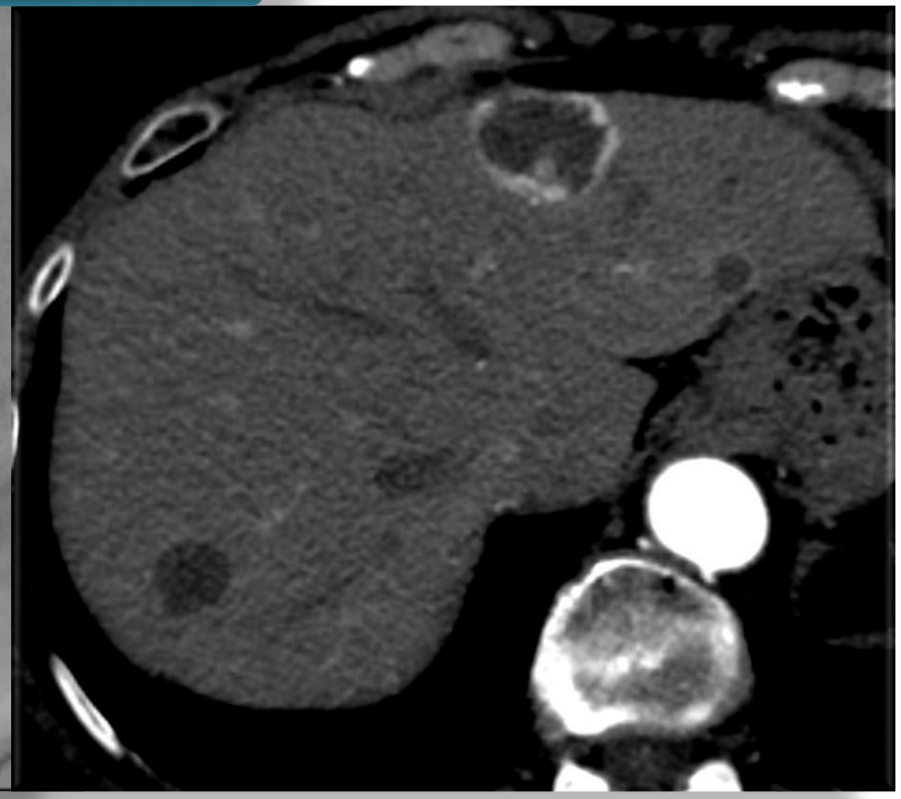
Technical effectiveness – Obtaining adequate Objective response by Imaging criteria (mRECIST)

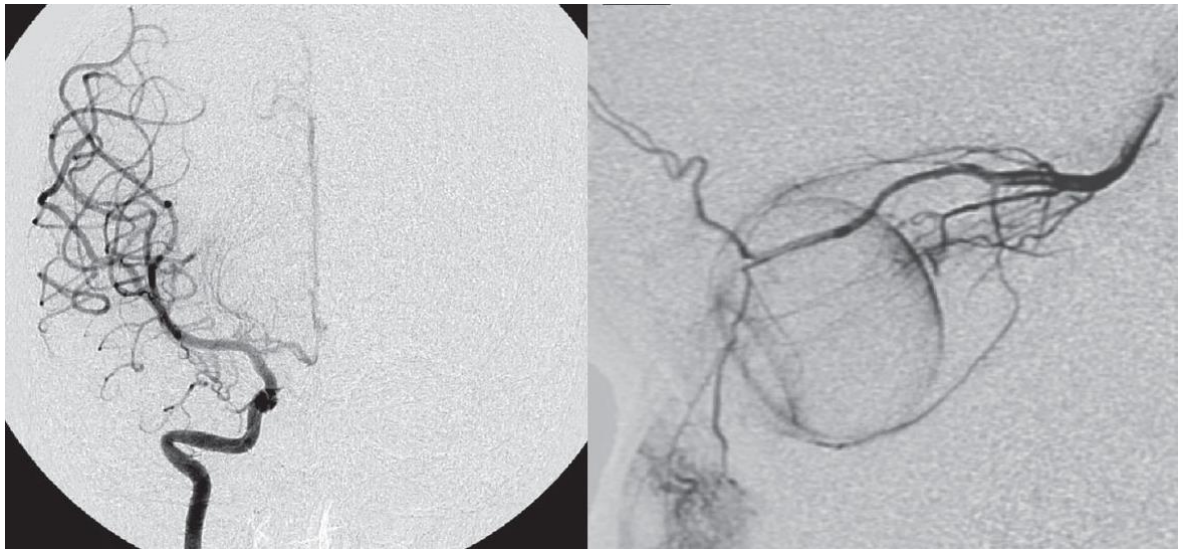
TARE









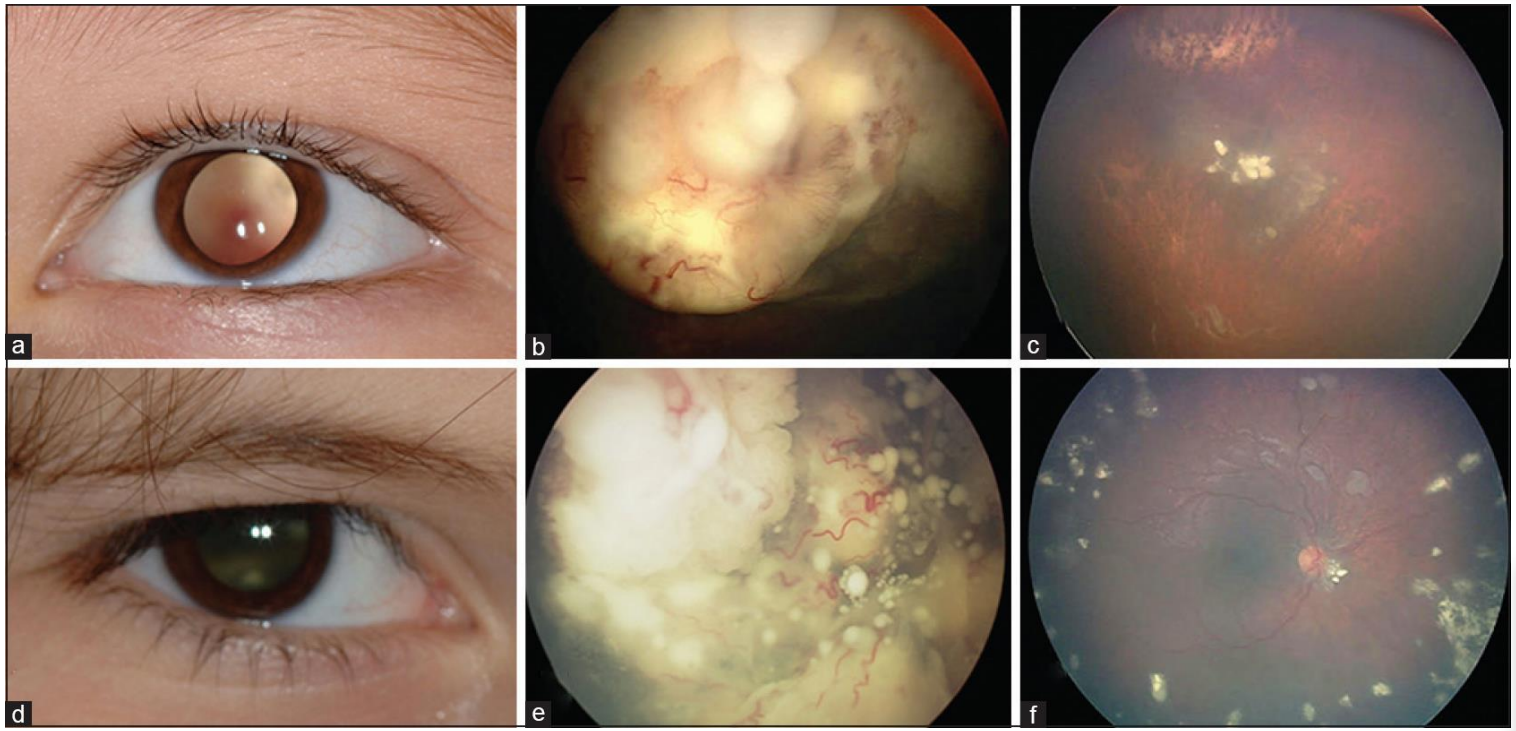


Clinical Success - Achieving the CInical goal

Personalized medicine and retinoblastoma treatment

Globe-salvaging therapies are minimizing the need for enucleation for the most common primary intraocular malignancy of childhood.

By Victor M. Villegas, MD, and Timothy G. Murray, MD, MBA, FACS



IAC-Retinoblastoma

Comparative Study > Indian J Ophthalmol. 2019 Dec;67(12):2005-2011.
doi: 10.4103/ijo.IJO_642_19.

Management of retinoblastoma in older children (>5 years) using intra-arterial chemotherapy: Comparison of outcomes to prechemotherapy and intravenous chemotherapy eras

Evan B Selzer [1], R Joel Welch [1], Pascal Jabbour [2], Ann M Leahey [3], Carol L Shields [1]

evidence
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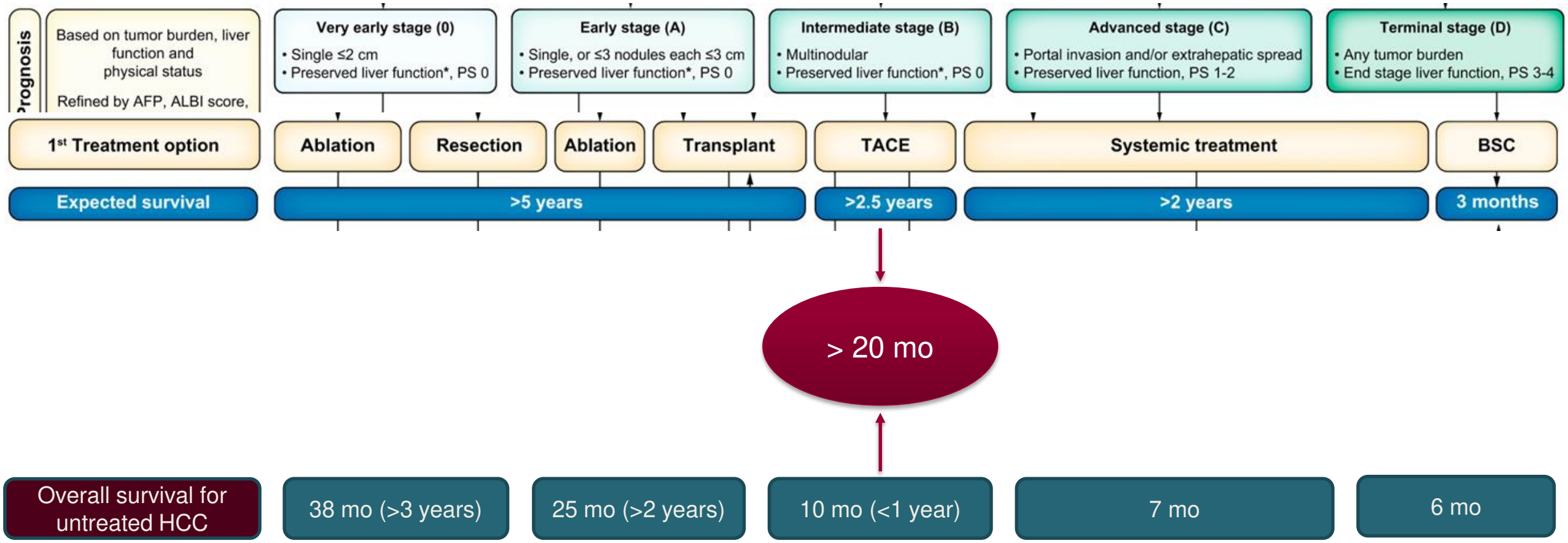
Survival benefit after TACE



Reig M, Forner A, Rimola J, Ferrer-Fàbrega J, Burrel M, Garcia-Criado Á, Kelley RK, Galle PR, Mazzaferro V, Salem R, Sangro B, Singal AG, Vogel A, Fuster J, Ayuso C, Bruix J. BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update. J Hepatol. 2022 Mar;76(3):681-693. doi: 10.1016/j.jhep.2021.11.018. Epub 2021 Nov 19. PMID: 34801630; PMCID: PMC8866082.

Giannini EG, Farinati F, Ciccarese F, Pecorelli A, Rapaccini GL, Di Marco M, Benvegnù L, Caturelli E, Zoli M, Borzio F, Chiaramonte M, Trevisani F; Italian Liver Cancer (ITA.LI.CA) group. Prognosis of untreated hepatocellular carcinoma. Hepatology. 2015 Jan;61(1):184-90. doi: 10.1002/hep.27443. Epub 2014 Nov 26. PMID: 25234419.

Benefits of intra-arterial therapies for HCC

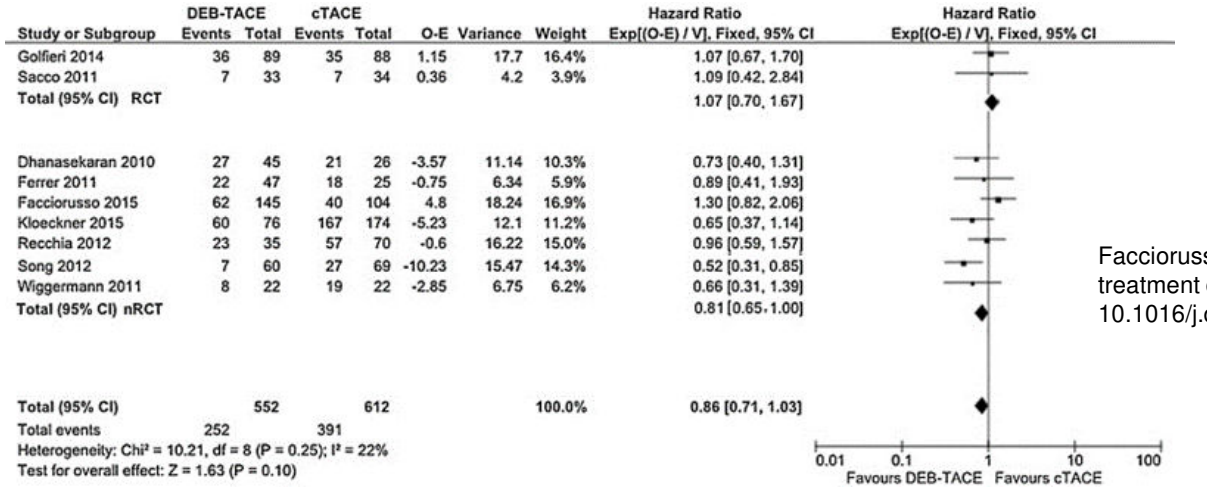
Response rates and survival are

cTACE = DEB-TACE[1]

PRECISION V - multicenter RCT phase II study, DEB-TACE & cTACE = Similar tumor response (p = 0.11).

PRECISION ITALIA STUDY GROUP phase III trial

No significant difference in tumor response, time to progression, and survival between cTACE and DEB-TACE[2]



Clinical Trial > Radiology. 2022 Jun;303(3):699-710. doi: 10.1148/radiol.211806. Epub 2022 Mar 8.

^{90}Y Radioembolization versus Drug-eluting Bead Chemoembolization for Unresectable Hepatocellular Carcinoma: Results from the TRACE Phase II Randomized Controlled Trial

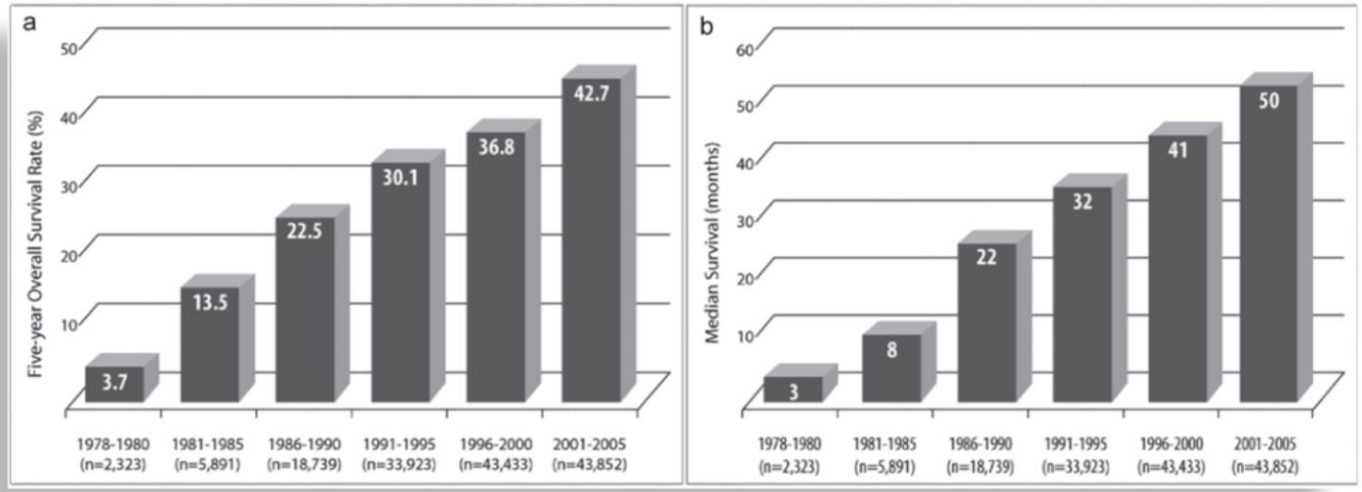
Elisabeth Dhondt [1], Bieke Lambert [1], Laurens Hermie [1], Lynn Huyck [1], Peter Vanlangenhove [1], Anja Geerts [1], Xavier Verhelst [1], Maridi Aerts [1], Aude Vanlander [1], Frederik Berrevoet [1], Roberto Ivan Troisi [1], Hans Van Vlierberghe [1], Luc Defreyne [1]

Median overall survival was 30.2 months after TARE and 15.6 months after DEB-TACE (ITT group HR, 0.48; 95% CI: 0.28, 0.82; P = .006).

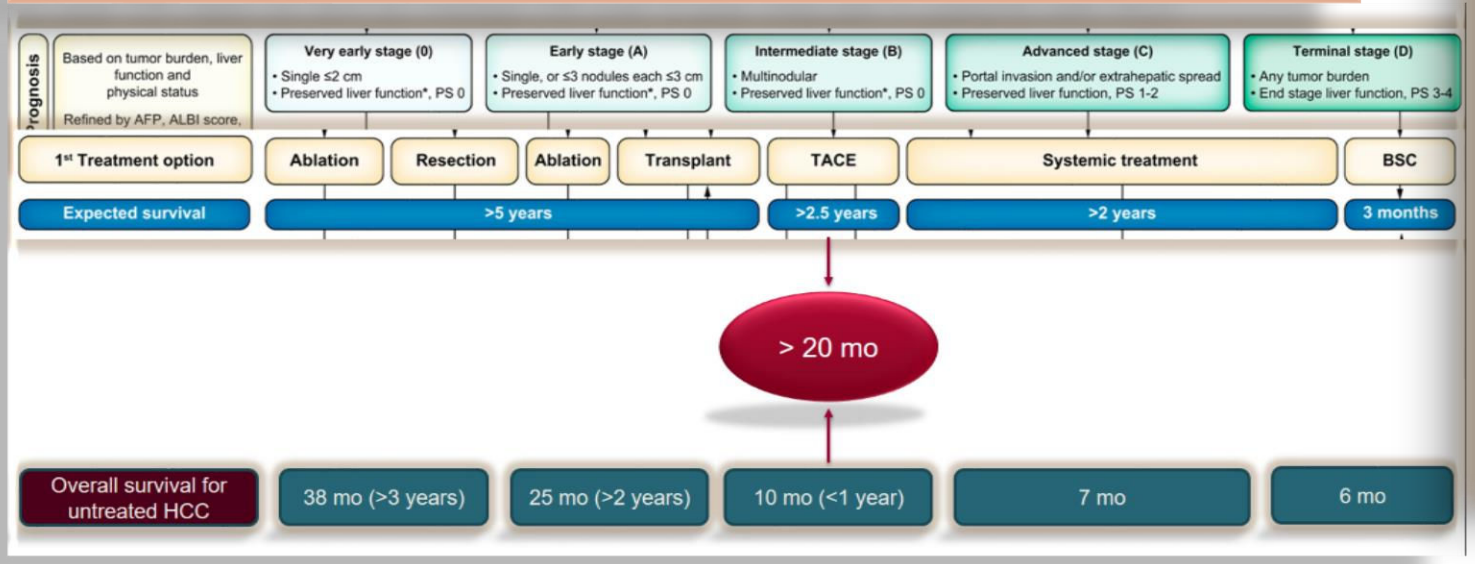
Facciorusso A, Di Maso M, Muscatiello N. Drug-eluting beads versus conventional chemoembolization for the treatment of unresectable hepatocellular carcinoma: A meta-analysis. Dig Liver Dis. 2016 Jun;48(6):571-7. doi: 10.1016/j.dld.2016.02.005. Epub 2016 Feb 21. PMID: 26965785.

1. Reig M, Forner A, Rimola J, Ferrer-Fàbrega J, Burrel M, Garcia-Criado Á, Kelley RK, Galle PR, Mazzaferro V, Salem R, Sangro B, Singal AG, Vogel A, Fuster J, Ayuso C, Bruix J. BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update. J Hepatol. 2022 Mar;76(3):681-693. doi: 10.1016/j.jhep.2021.11.018. Epub 2021 Nov 19. PMID: 34801630; PMCID: PMC8866082.
2. Chang Y, Jeong SW, Young Jang J, Jae Kim Y. Recent Updates of Transarterial Chemoembolilzation in Hepatocellular Carcinoma. Int J Mol Sci. 2020 Oct 31;21(21):8165. doi: 10.3390/ijms21218165. PMID: 33142892; PMCID: PMC7662786.

Survival benefit for HCC



Five-year OS rates (a) and (b) median OS over 5-year intervals in patients with HCC



› Liver Cancer. 2016 Jul;5(3):190-7. doi: 10.1159/000367775. Epub 2016 May 10.

Survival Analysis over 28 Years of 173,378 Patients with Hepatocellular Carcinoma in Japan

Masatoshi Kudo [1], Namiki Izumi [2], Michiie Sakamoto [3], Yutaka Matsuyama [4], Takafumi Ichida [5], Osamu Nakashima [6], Osamu Matsui [7], Yonson Ku [8], Norihiro Kokudo [9], Masatoshi Makuuchi [10]; Liver Cancer Study Group of Japan

Table 2. Five-year OS rates (%) in patients who underwent resection, ablation, TACE, and HAIC assorted by year of initial diagnosis

	Resection (n=42,713)		Ablation (n=37,196)		TACE (n=61,460)		HAIC (n=14,246)	
	n	5-year OS rate,%	n	5-year OS rate,%	n	5-year OS rate,%	n	5-year OS rate,%
1978–1980	505	14.5			93	5.4	889	2.5
1981–1985	2,363	28.7*			1,682	17.8*	1,755	8.3*
1986–1990	5,959	40.5*	1,962	32.8	8,423	22.3*	1,82[illegible]	14.6*
1991–1995	9,822	49.5*	7,246	37.7*	14,80[illegible]	26.2*	1,079	16.0
1996–2000	11,562	54.5*	12,923	43.1*	18,037	30.5*	3,198	32.0*
2001–2005	12,502	58.4*	15,065	47.6*	18,419	35.0*	5,504	31.9

*p<0.0001 compared with the preceding time period.

Table 3. Median OS (months) in patients who underwent resection, ablation, TACE, and HAIC assorted by year of initial diagnosis

	Resection (n=42,713)		Ablation (n=37,196)		TACE (n=61,460)		HAIC (n=14,246)	
	n	Median OS, months	n	Median OS, months	n	Median OS, months	n	Median OS, months
1978–1980	505	13			93	9	889	4
1981–1985	2,363	28			1,682	17	1,755	7
1986–1990	5,959	46	1,962	41	8,423	27	1,82[illegible]	12
1991–1995	9,822	60	7,246	47	14,806	32	1,079	10
1996–2000	11,562	69	12,923	53	18,037	37	3,198	33
2001–2005	12,502	74	15,065	59	18,419	42	5,504	31

Reig M, Forner A, Rimola J, Ferrer-Fàbrega J, Burrel M, Garcia-Criado Á, Kelley RK, Galle PR, Mazzaferro V, Salem R, Sangro B, Singal AG, Vogel A, Fuster J, Ayuso C, Bruix J. BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update. J Hepatol. 2022 Mar;76(3):681-693. doi: 10.1016/j.jhep.2021.11.018. Epub 2021 Nov 19. PMID: 34801630; PMCID: PMC8866082.

Giannini EG, Farinati F, Ciccarese F, Pecorelli A, Rapaccini GL, Di Marco M, Benvegnù L, Caturelli E, Zoli M, Borzio F, Chiaramonte M, Trevisani F; Italian Liver Cancer (ITA.LI.CA) group. Prognosis of untreated hepatocellular carcinoma. Hepatology. 2015 Jan;61(1):184-90. doi: 10.1002/hep.27443. Epub 2014 Nov 26. PMID: 25234419.

cTACE or DEB-TACE??

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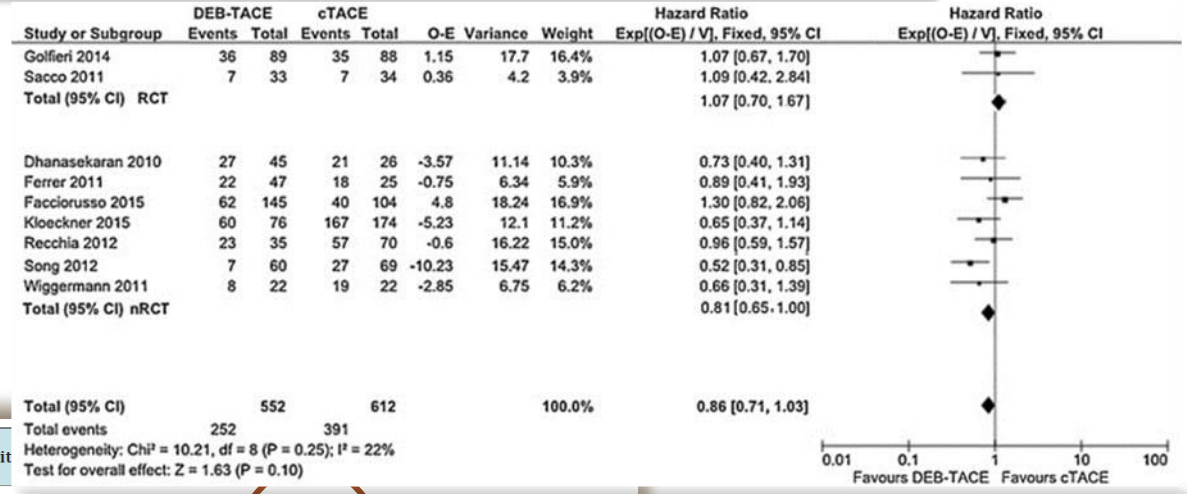


	Type	DEM-TACE/c-TACE Numbers	Child-Pugh A/B/C (%)	BCLC A/B/C (%)	Crit			
Lammer et al. 2010 (26)	P	93 vs. 108	82.8/17.2/0 vs. 82.4/17.6/0	25.8/74.2/0 vs. 26.9/73.1/0	EASL	51.6 vs. 43.5	N/A	N/A
Dhanasekaran et al. 2010 (33)	R	45 vs. 26	48.9/24.4/26.7 vs. 42.3/42.3/15.4	N/A	N/A	N/A	20.3/0 vs. 13.4/0	N/A
Ferrer Puchol et al. 2011 (60)	P	47 vs. 25	Both group 87.5/12.5/0	N/A	RECIST	36.1 vs. 15.3	22.4/25.5 vs. 23.6/22.9	N/A
Song et al. 2012 (59)	R	60 vs. 69	93.3/6.7/0 vs. 89.9/10.1/0	45/55/0 vs. 40.6/59.4/0	mRECIST	81.6 vs. 49.4	0/32.2 vs. 0/24.7	1 y 88% vs. 67%
Kloeckner et al. 2015 (61)	R	76 vs. 174	67.1/28.9/3.9 vs. 59.2/36.8/4	10.5/44.7/ 39.5/5.3 vs. 17.2/33.9/ 44.3/4.6	N/A	N/A	12.3/0 vs. 13.6/0	N/A
Kucukay et al. 2015 (62)	R	53 vs. 73	N/A	54.7/35.8/9.6 vs. 39.7/54.8/5.5	N/A	N/A	0/37.4 vs. 0/39	1 y 95.9% vs. 84.9% 2 y 92.3% vs. 74.6%
Arabi et al. 2015 (63)	R	35 vs. 25	68/32/0 vs. 88/12/0	N/A	mRECIST	35 vs. 36	N/A	2 y 58% vs. 60%
Megías Vericat et al. 2015 (64)	R	30 vs. 30	46.7/53.3/0 vs. 66.7/33.3/0	N/A	N/A	N/A	N/A	5 y 20% vs. 30%
Rahman et al. 2016 (65)	R	45 vs. 34	N/A	20/80/0 vs. 32/68/0	mRECIST	39 vs. 29	8.3/0 vs. 4.9/0	N/A
Baur et al. 2016 (66)	R	14 vs. 18	78.6/21.4/0 vs. 58.8/29.7/11.8	N/A	N/A	N/A	9.2/0 vs. 10.8/0	N/A
Massani et al. 2017 (67)	R	28 vs. 54	85.7/14.3/0 vs. 83.3/16.7/0	10.7/14.3/75 vs. 18.5/50/31.5	N/A	N/A	22.7/29.4 vs. 21.8/27	N/A
Lee et al. 2017 (68)	R	106 vs. 144	80.2/19.8/0 vs. 66.0/34.0/0	18.9/72.6/8.5 vs. 34/50.7/15.3	mRECIST	86.8 vs. 78.3	46.6/0 vs. 44.9/0	N/A

Facciorusso A, Di Maso M, Muscatiello N. Drug-eluting beads versus conventional chemoembolization for the treatment of unresectable hepatocellular carcinoma: A meta-analysis. Dig Liver Dis. 2016 Jun;48(6):571-7. doi: 10.1016/j.dld.2016.02.005. Epub 2016 Feb 21. PMID: 26965785.

Nouri YM, Kim JH, Yoon HK, Ko HK, Shin JH, Gwon DI. Update on Transarterial Chemoembolization with Drug-Eluting Microspheres for Hepatocellular Carcinoma. Korean J Radiol. 2019 Jan;20(1):34-49. doi: 10.3348/kjr.2018.0088. Epub 2018 Dec 27. PMID: 30627020; PMCID: PMC6315076.

1. Reig M, Forner A, Rimola J, Ferrer-Fàbrega J, Burrel M, Garcia-Criado Á, Kelley RK, Galle PR, Mazzaferro V, Salem R, Sangro B, Singal AG, Vogel A, Fuster J, Ayuso C, Bruix J. BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update. J Hepatol. 2022 Mar;76(3):681-693. doi: 10.1016/j.jhep.2021.11.018. Epub 2021 Nov 19. PMID: 34801630; PMCID: PMC8866082.
2. Chang Y, Jeong SW, Young Jang J, Jae Kim Y. Recent Updates of Transarterial Chemoembolilzation in Hepatocellular Carcinoma. Int J Mol Sci. 2020 Oct 31;21(21):8165. doi: 10.3390/ijms21218165. PMID: 33142892; PMCID: PMC7662786.

Table 6. Thresholds for Median Survival for Various Tumor Pathologies from Time of Transarterial Chemoembolization or Embolization

Tumor	Median Survival (months)	Representative References	Suggested Threshold (%)*
HCC	20	(8–11,13–15, 96–98,100)	50
ICC	15	(106),†	50
Metastatic NET	26	(107),*	50
CLM	10	(55–57,112–114,116)	50
Metastatic uveal melanoma‡	10	(31,117–120)	50
Metastatic sarcoma	19	(122,123)	50

STANDARDS OF PRACTICE

Quality Improvement Guidelines for Transarterial Chemoembolization and Embolization of Hepatic Malignancy

Ron C. Gaba, MD, R. Peter Lokken, MD, MPH, Ryan M. Hickey, MD, ıdrew J. Lipnik, MD, Robert J. Lewandowski, MD, Riad Salem, MD, MBA, Daniel B. Brown, MD, T. Gregory Walker, MD, James E. Silberzweig, MD, Mark Otto Baerlocher, MD, Ana Maria Echenique, MD, Mehran Midia, MD, Jason W. Mitchell, MD, MPH, MBA, Siddharth A. Padia, MD, Suvranu Ganguli, MD, Thomas J. Ward, MD, Jeffrey L. Weinstein, MD, Boris Nikolic, MD, MBA, and Sean R. Dariushnia, MD, for the Society of Interventional Radiology Standards of Practice Committee

Risks and Complications

Major complication incidence
2.1% (24/1120) per patient
0.84% (24/2863) per TAE/TACE procedure.

Major complications
8.1% per patient
4.9% per procedure

Minor: Postembolization syndrome 71 (20%) patients

Medicine (Baltimore). 2016 Dec; 95(49): e5606. PMCID: PMC5266057
Published online 2016 Dec 9. doi: 10.1097/MD.0000000000005606 PMID: 27930585

The incidence and outcome of major complication following conventional TAE/TACE for hepatocellular carcinoma

Jianfei Tu, MD,[a] Zhongzhi Jia, PhD,[b] Xihui Ying, MD,[a] Dengke Zhang, MD,[a] Shaoqin Li, MD,[b] Feng Tian, MD,[b] and Guomin Jiang, MD[b,*]

Cir Esp (Engl Ed). 2018 Nov;96(9):560-567. doi: 10.1016/j.ciresp.2018.06.004. Epub 2018 Aug 3.

Complications of transarterial chemoembolization (TACE) in the treatment of liver tumors

[Article in English, Spanish]

Alberto Marcacuzco Quinto [1], Oana-Anisa Nutu [2], Ricardo San Román Manso [3], Iago Justo Alonso [2], Jorge Calvo Pulido [2], Alejandro Manrique Municio [2], Álvaro García-Sesma [2], Carmelo Loinaz Segurola [2], Javier Martínez Caballero [2], Luis Carlos Jiménez Romero [2]

Outcome for Retinoblastoma – Risk/benefit

2-year radiation-free ocular survival rate is **86 – 90%**

Early intraocular disease (Group B and C eyes) - ocular salvage rates exceeding **85%**.

Group D eyes - ocular salvage rates **>80%** have been reported in specialized centers.

For patients with very advanced intraocular disease – systemic chemotherapy followed by consolidation with intra-arterial melphalan

Salvage treatment for patients with recurrent or progressive disease - globe survival rates **50-75%**

Complications related to intra-arterial chemotherapy

- Retinal detachment (up to 19.3%).
- Vitreous hemorrhage (up to 18.1%)
- Ptosis (13.6%)
- Dysmotility (6.5%)
- Vascular and ischemic effects, including ophthalmic artery occlusion (up to 9%)
- Optic atrophy (3.4%)
- Phthisis (2.7%)

https://www.cancer.gov/types/retinoblastoma/hp/retinoblastoma-treatment-pdq 29/62

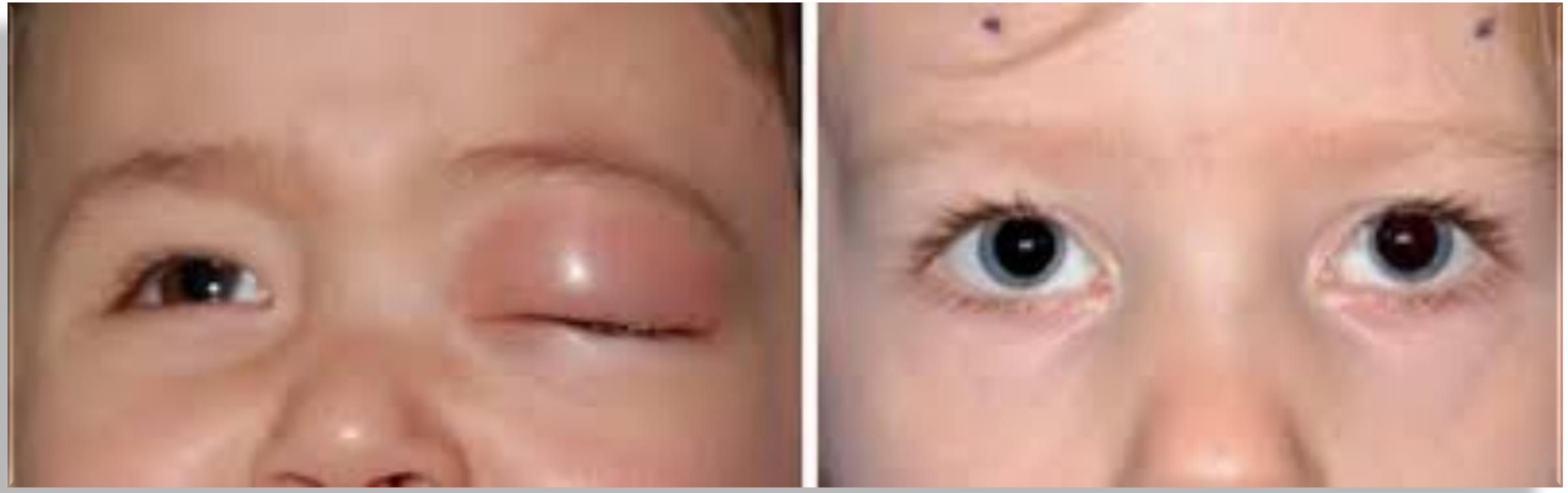
Key outcomes of the widespread adoption of IAC / OAC

- 1. Eliminating the use of EBRT,
- 2. Eliminating the use of systemic multiagent chemotherapy
- a. Likely eliminating the development of secondary leukemia
- b. Reducing expense
- c. Reduced impact on immune function,
- d. Avoiding associated hindrance of patient growth (height and weight)

Schaiquevich P, Francis JH, Cancela MB, Carcaboso AM, Chantada GL, Abramson DH. Treatment of Retinoblastoma: What Is the Latest and What Is the Future. Front Oncol. 2022 Apr 1;12:822330. doi: 10.3389/fonc.2022.822330. PMID: 35433448; PMCID: PMC9010858.

- 3. increasing the rate of eye salvage. At MSKCC, this rate has increased from 5 to 95% (42).
- 4. Enabling salvage of eyes that have failed multiagent systemic chemotherapy
- 5. Reducing the time from initiating to completing therapy (2).
- 6. Successful treatment of choroidal invasion, orbital retinoblastoma and optic nerve invasion in select cases (43, 44).
- 7. Enabling cure of eyes with vitreous and or subretinal seeding which was nearly impossible with systemic chemotherapy and usually failed with external beam radiation.
- 8. Avoidance of increased risk of orbital disease or second cancers (45).
- 9. Allowing almost 25% of all eyes with retinal detachment and extinguished ERGs to regain more than 25 µV of activity (46).

A life is always worth saving ☺

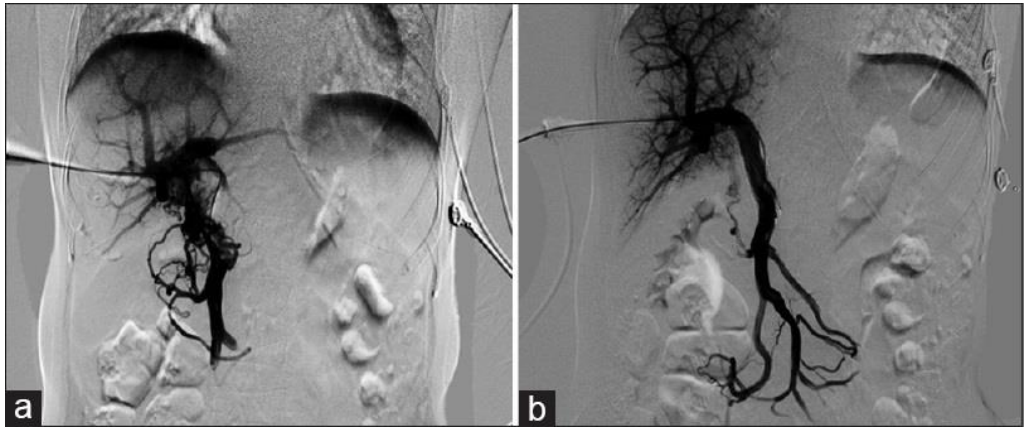


› Arch Ophthalmol. 2011 Nov;129(11):1407-15. doi: 10.1001/archophthalmol.2011.151. Epub 2011 Jun 13.

Intra-arterial chemotherapy for retinoblastoma: report No. 2, treatment complications

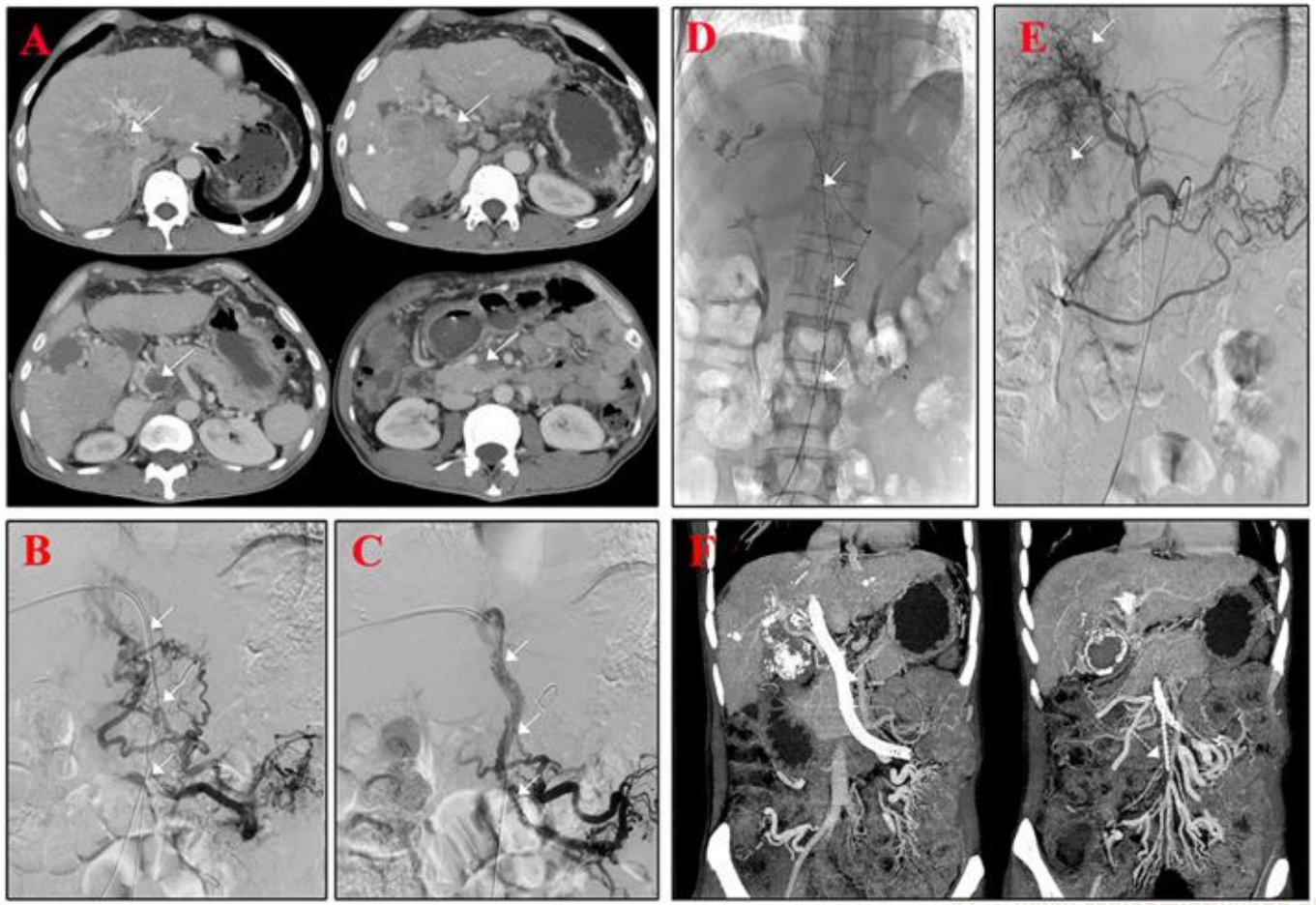
Carol L Shields [1], Carlos G Bianciotto, Pascal Jabbour, Gregory C Griffin, Aparna Ramasubramanian, Robert Rosenwasser, Jerry A Shields

Vascular Palliative therapies in Oncology



Chen ZW, Lin ZY, Chen YP, Chen J, Chen J. Clinical efficacy of endovascular radiofrequency ablation in the treatment of portal vein tumor thrombus of primary hepatocellular carcinoma. J Cancer Res Ther. 2018 Jan;14(1):145-149. doi: 10.4103/jcrt.JCRT_784_17. PMID: 29516977.

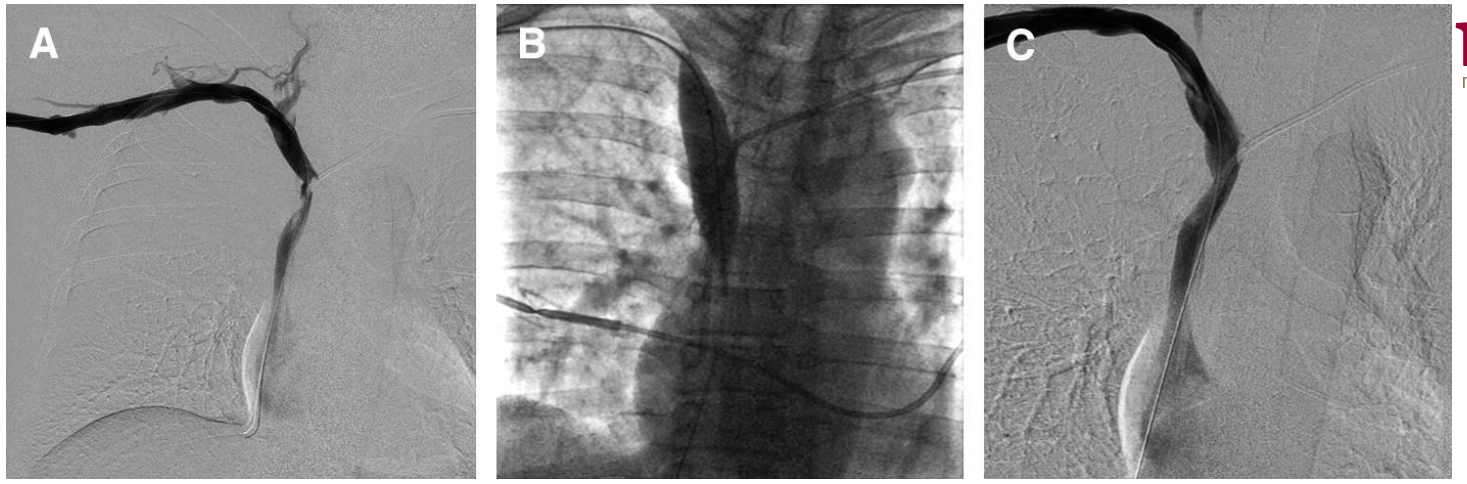
1. Tumor control / Symptom control – Embo/Chemo-embo
2. Endovascular RFA & Brachytherapy – PV tumor thrombus



Desai KR, Chen RI. Endovascular therapy for palliative care of cancer patients. Semin Intervent Radiol. 2007 Dec;24(4):382-90. doi: 10.1055/s-2007-992326. PMID: 21326590; PMCID: PMC3037249.

Li L, Cheng N, Huang X, Weng X, Jiao Y, Liu J, Guo W. Efficacy and safety of endovascular brachytherapy combined with transarterial chemoembolization for the treatment of hepatocellular carcinoma patients with type III or IV portal vein tumor thrombosis. World J Surg Oncol. 2022 Feb 2;20(1):30. doi: 10.1186/s12957-022-02495-4. PMID: 35109883; PMCID: PMC8808970.

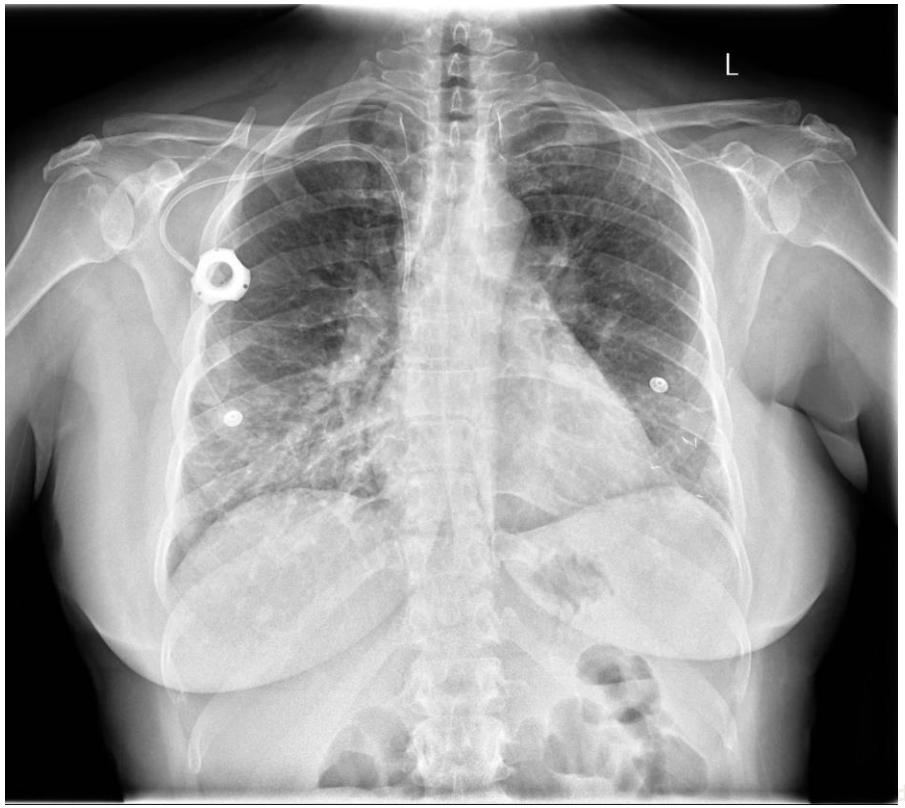
Vascular Palliative therapies in Oncology



Rachapalli V, Boucher LM. Superior vena cava syndrome: role of the interventionalist. Can Assoc Radiol J. 2014 May;65(2):168-76. doi: 10.1016/j.carj.2012.09.003. Epub 2013 Feb 14. PMID: 23415716.

3. Stenting for SVC syndrome, Iliac vein

4. Placement of intravenous (IV) access.



Desai KR, Chen RI. Endovascular therapy for palliative care of cancer patients. Semin Intervent Radiol. 2007 Dec;24(4):382-90. doi: 10.1055/s-2007-992326. PMID: 21326590; PMCID: PMC3037249.

https://medschool.co/tests/chest-xray/confirming-central-venous-access-position


New Horizons

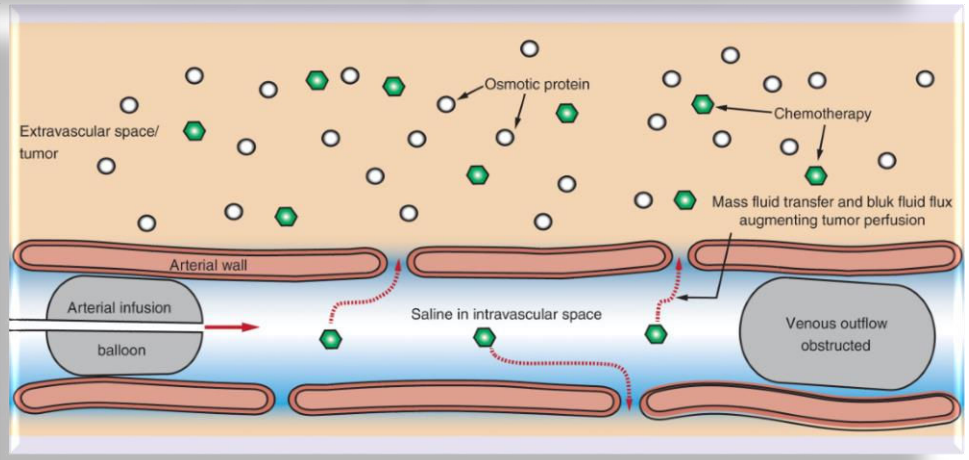
Future?

New Delivery Mechanisms

Acta Radiol. 2016 Jul;57(7):844-51. doi: 10.1177/0284185115603246. Epub 2015 Sep 3.

Combination of radiofrequency ablation with transarterial chemoembolization for treatment of hepatocellular carcinoma: experience from a Danish tertiary liver center

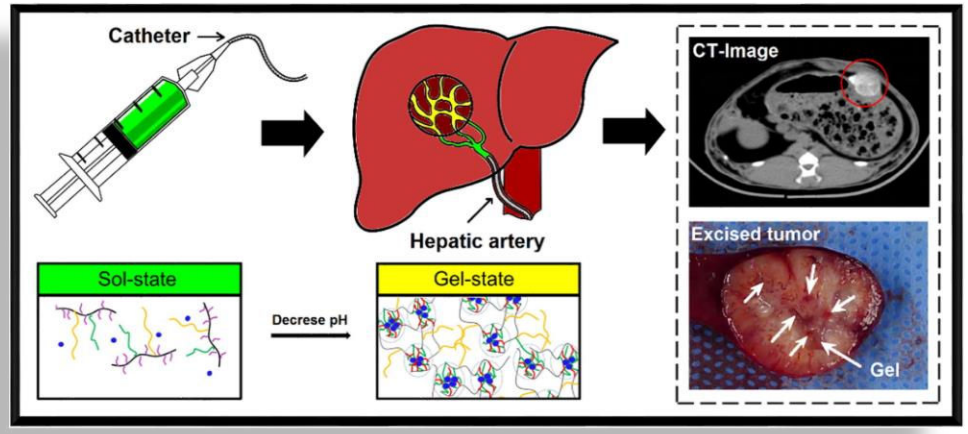
Arindam Bharadwaz [1], Kirstine Petrea Bak-Fredslund [2], Gerda Elisabeth Villadsen [2], Jens Erik Nielsen [3], Kira Simonsen [2], Thomas Damgaard Sandahl [2], Henning Grønbæk [2], Dennis Tønner Nielsen [3]



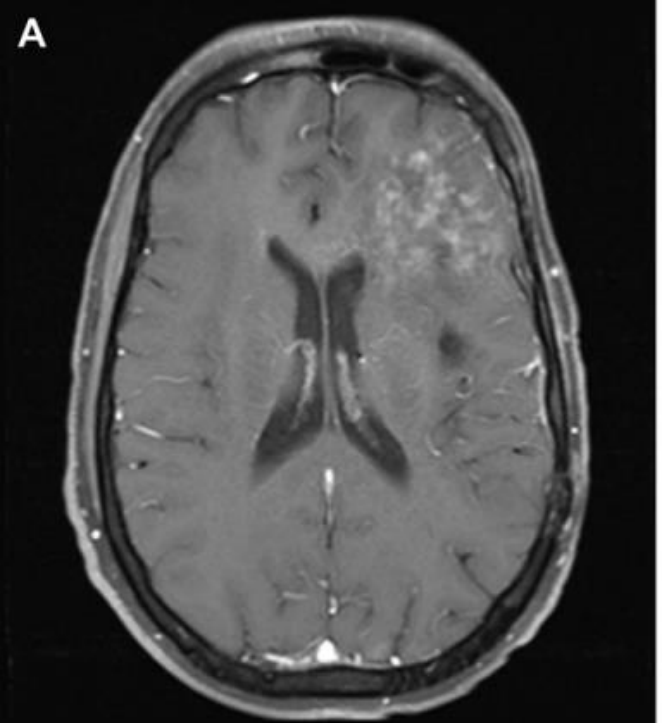
Lane RJ, Khin NY, Pavlakis N, Hugh TJ, Clarke SJ, Magnussen J, Rogan C, Flekser RL. Challenges in chemotherapy delivery: comparison of standard chemotherapy delivery to locoregional vascular mass fluid transfer. Future Oncol. 2018 Mar;14(7):647-663. doi: 10.2217/fon-2017-0546. Epub 2018 Mar 7. PMID: 29513086.

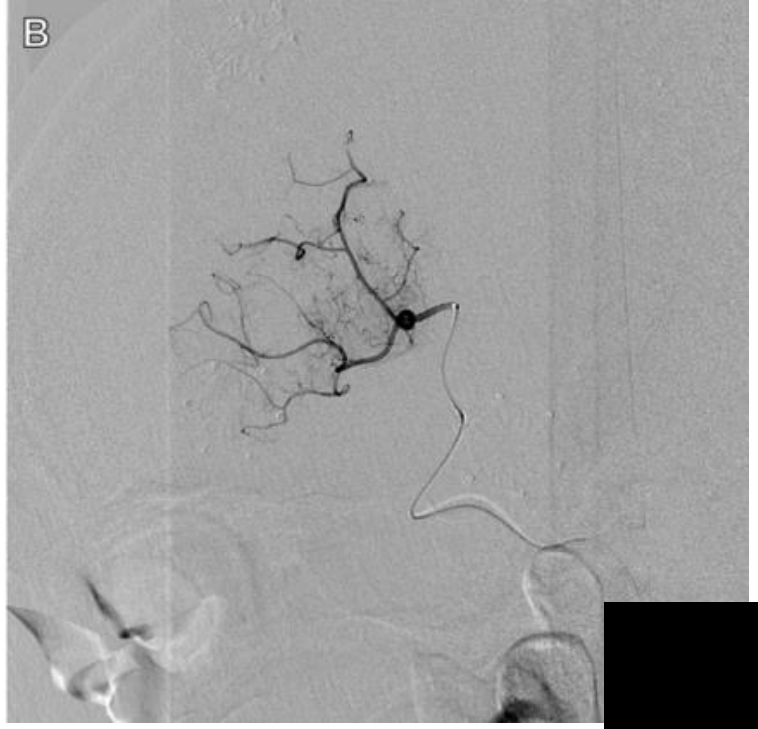
Combination therapy

- TACE with Ablation
- TACE with Radiation Therapy
- TACE with Systemic Chemotherapy
- TACE with combination of immune therapy

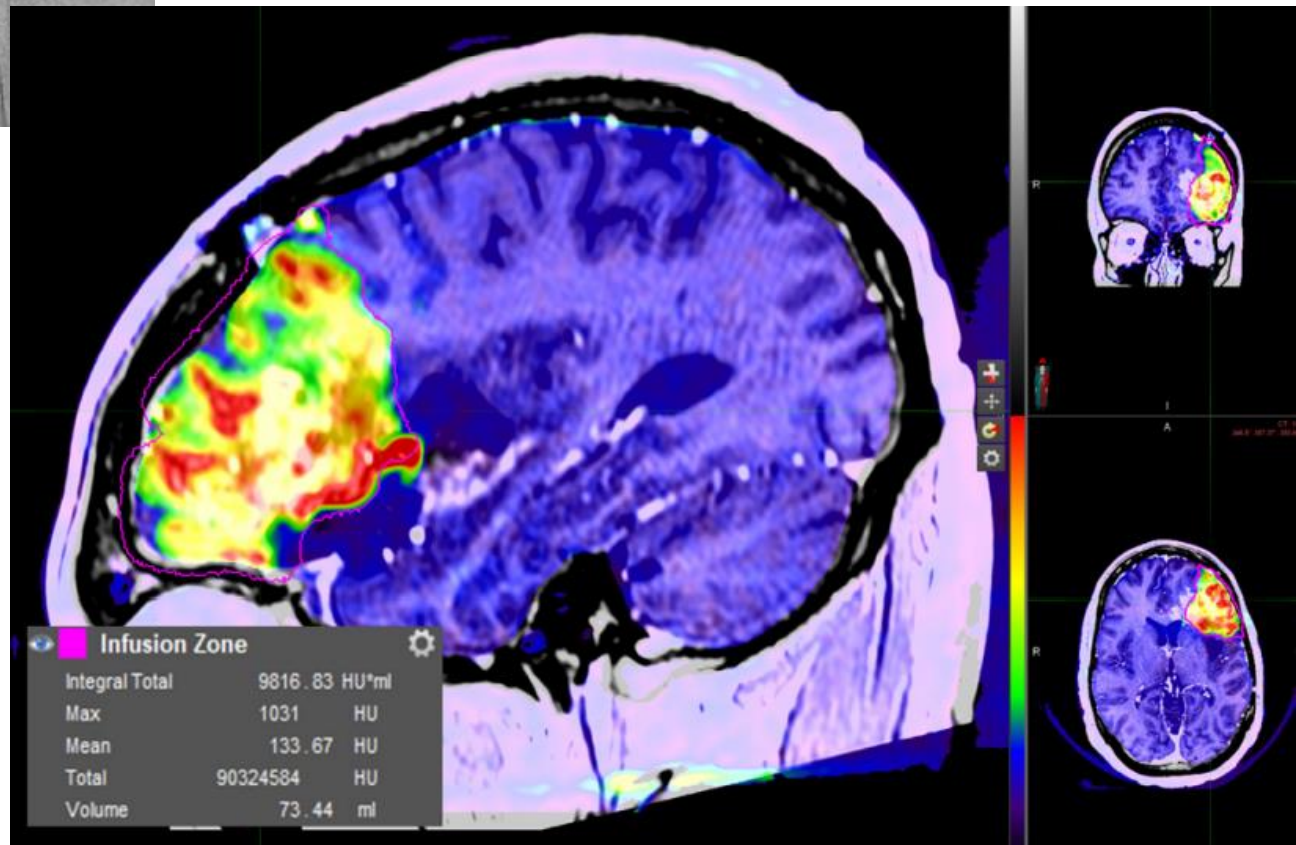


Lym JS, Nguyen QV, Ahn da W, Huynh CT, Jae HJ, Kim YI, Lee DS. Sulfamethazine-based pH-sensitive hydrogels with potential application for transcatheter arterial chemoembolization therapy. Acta Biomater. 2016 Sep 1;41:253-63. doi: 10.1016/j.actbio.2016.05.018. Epub 2016 May 13. PMID: 27184404.





New horizon – Brain Tumors Image fusion guided Intra-arterial therapies

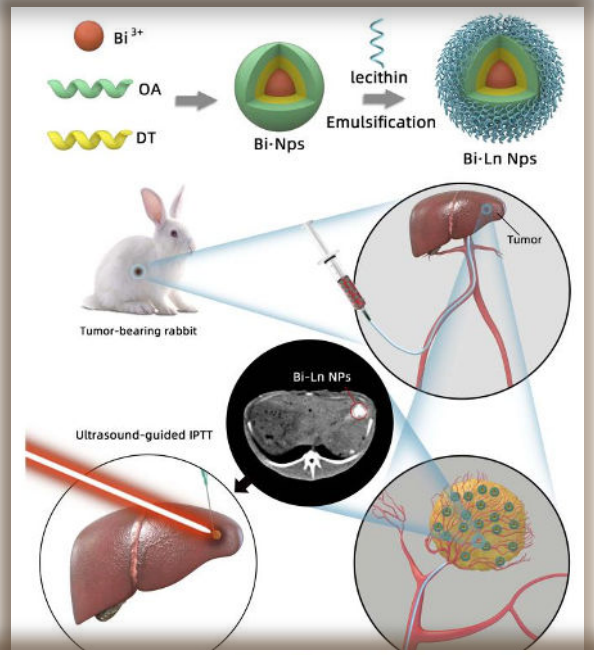


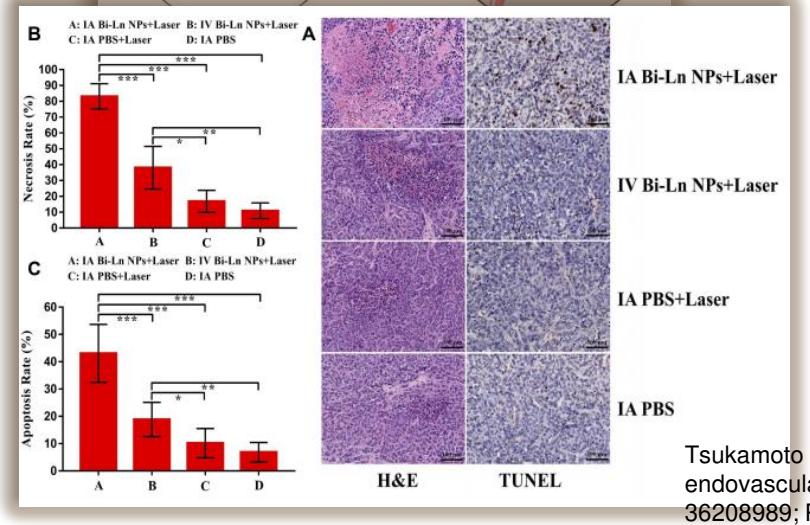
Chen SR, Chen MM, Ene C, Lang FF, Kan P. Perfusion-guided endovascular super-selective intra-arterial infusion for treatment of malignant brain tumors. J Neurointerv Surg. 2022 Jun;14(6):533-538. doi: 10.1136/neurintsurg-2021-018190. Epub 2021 Nov 25. PMID: 34824133.

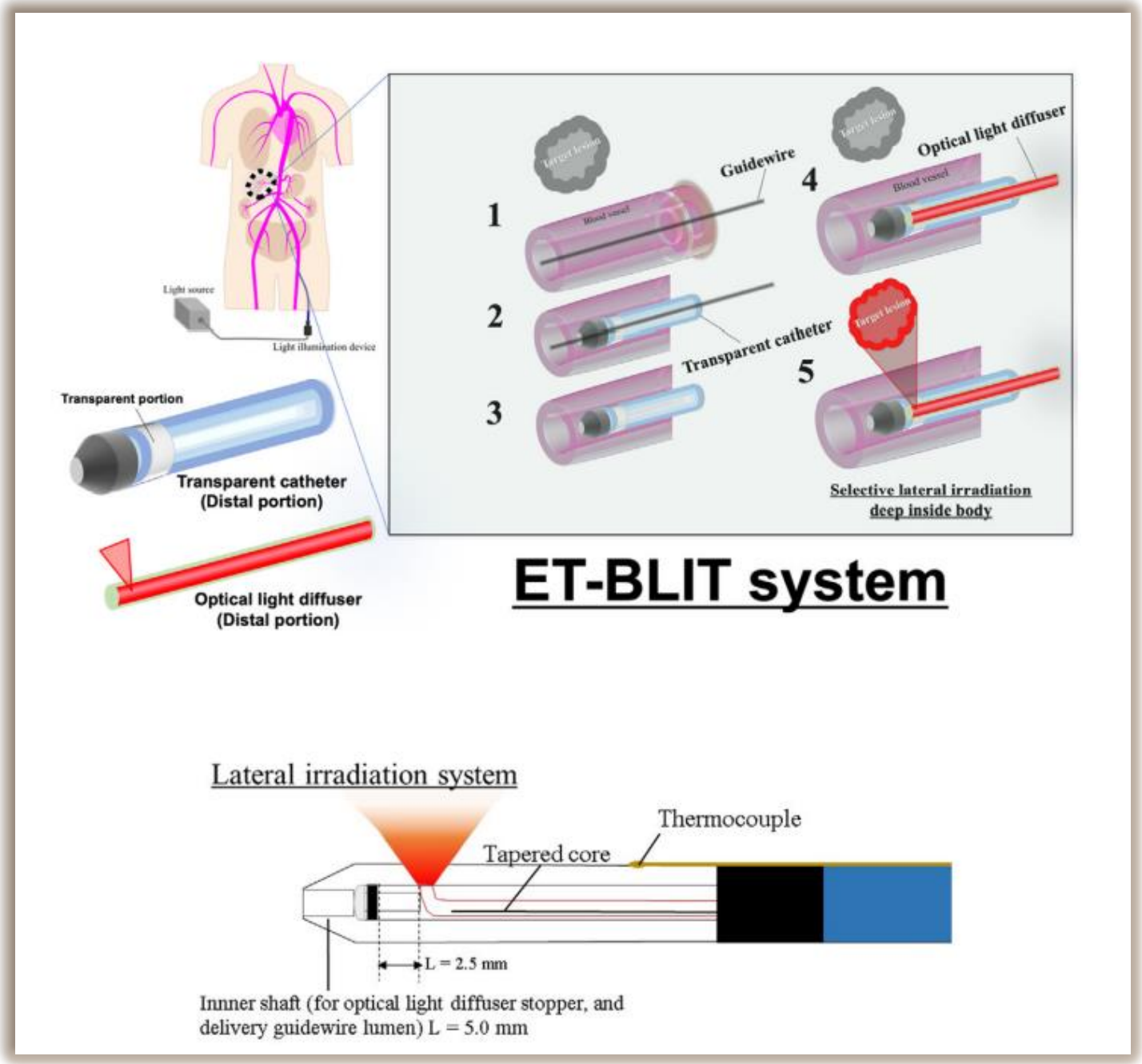
Int J Nanomedicine. 2020 Feb 28;15:1373-1385. doi: 10.2147/IJN.S233989. eCollection 2020.

Transcatheter Intra-Arterial Infusion Combined with Interventional Photothermal Therapy for the Treatment of Hepatocellular Carcinoma

Jun Zhou [1], Gonghao Ling [1], Jia Cao [1], Xun Ding [1], Xingnan Liao [1], Meng Wu [2], Xinyu Zhou [3], Haibo Xu [1], QingYun Long [1]

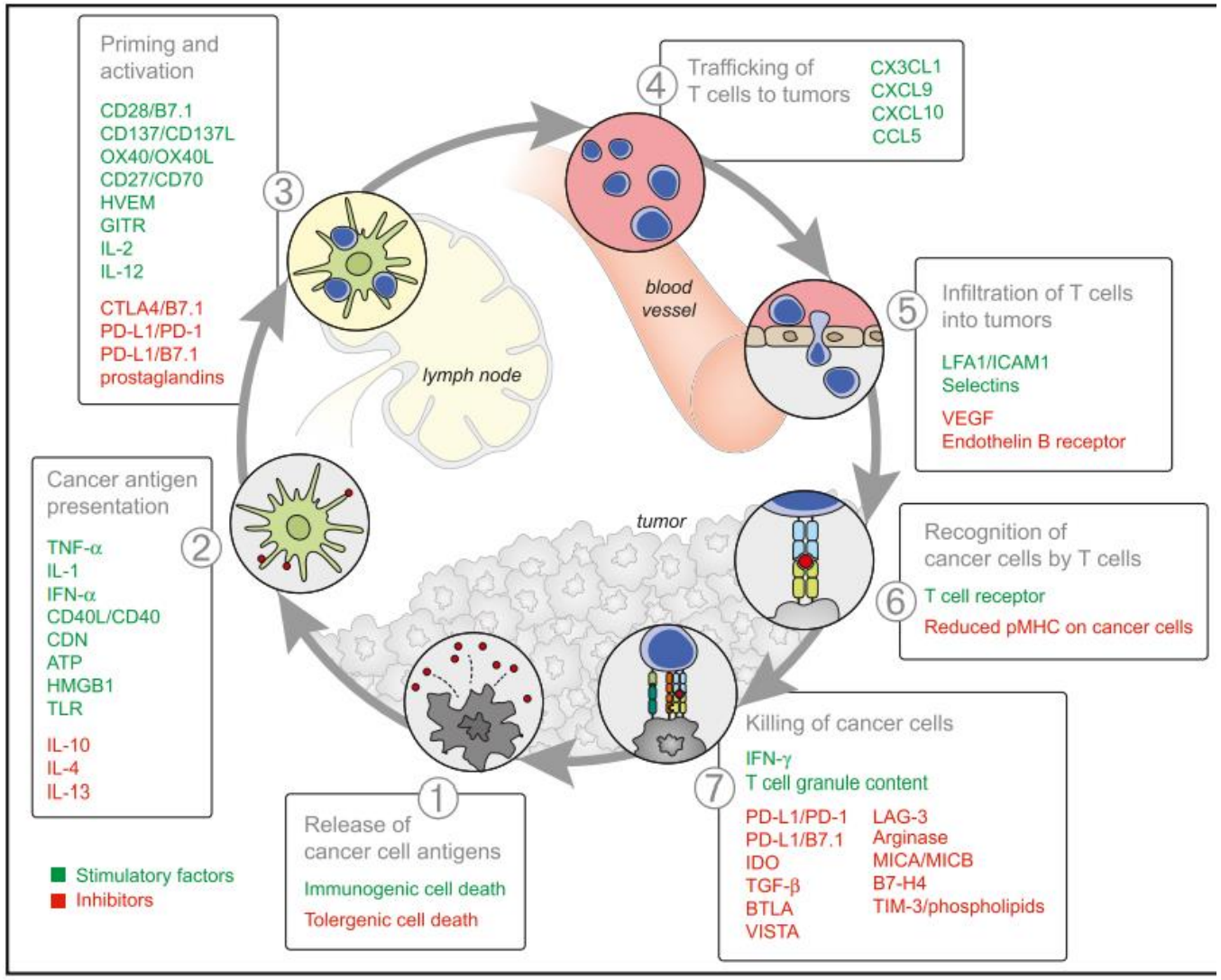




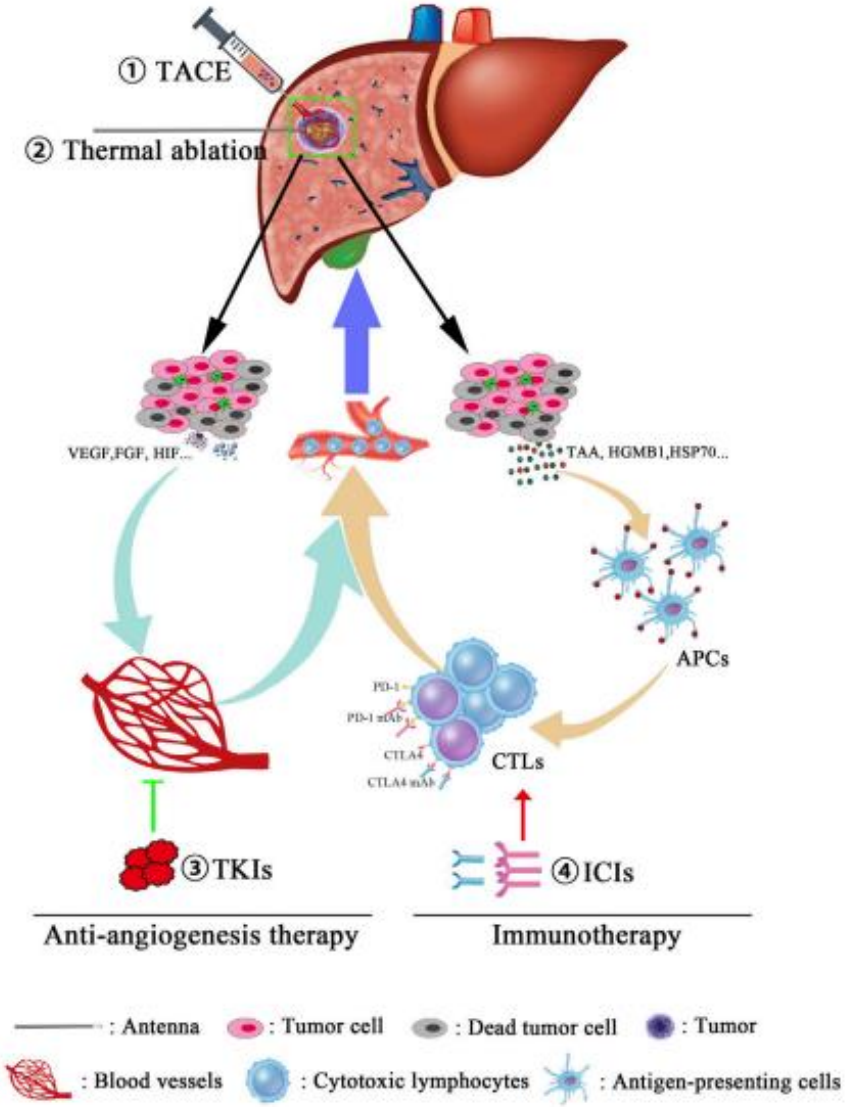


Tsukamoto T, Fujita Y, Shimogami M, Kaneda K, Seto T, Mizukami K, Takei M, Isobe Y, Yasui H, Sato K. Inside-the-body light delivery system using endovascular therapy-based light illumination technology. EBioMedicine. 2022 Nov;85:104289. doi: 10.1016/j.ebiom.2022.104289. Epub 2022 Oct 5. PMI 36208989; PMCID: PMC9669774.

Combination – Vascular therapy & Cancer Immunotherapy

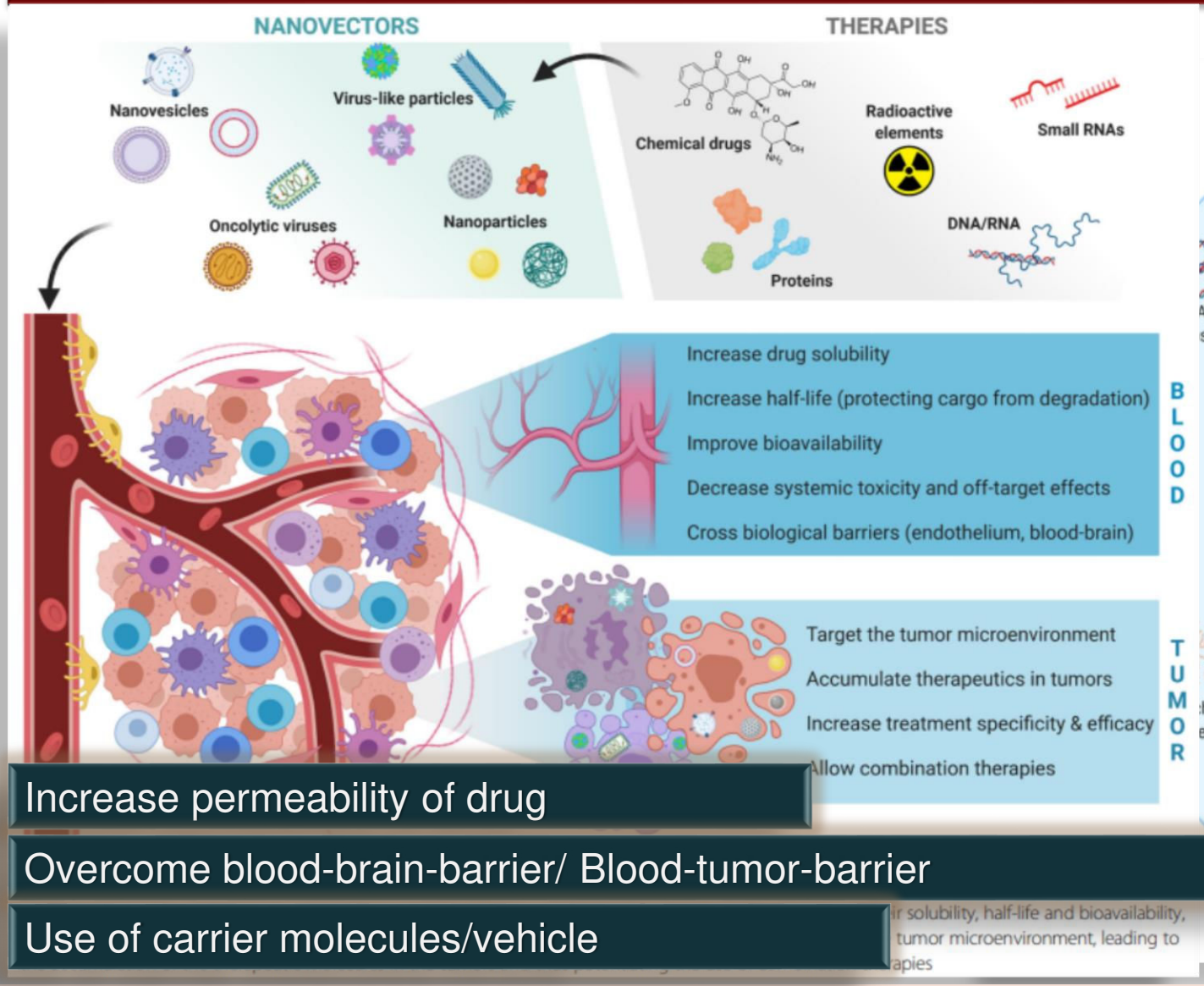


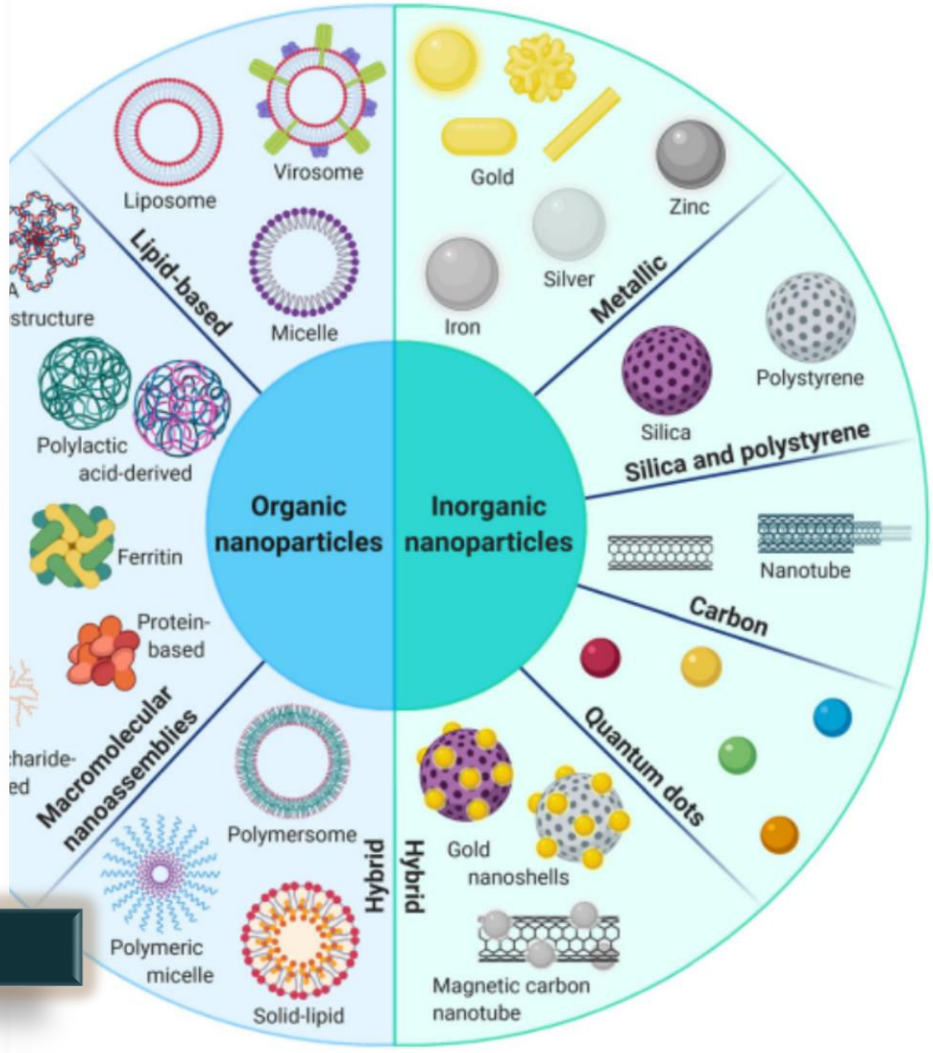
Chen DS, Mellman I. Oncology meets immunology: the cancer-immunity cycle. Immunity. 2013 Jul 25;39(1):1-10. doi: 10.1016/j.immuni.2013.07.012. PMID: 23890059.



Li X, Wang Y, Ye X, Liang P. Locoregional Combined With Systemic Therapies for Advanced Hepatocellular Carcinoma: An Inevitable Trend of Rapid Development. Front Mol Biosci. 2021 Apr 13;8:635243. doi: 10.3389/fmolb.2021.635243. PMID: 33928118; PMCID: PMC8076864.

Newcomers in the horizon 2 - Agents





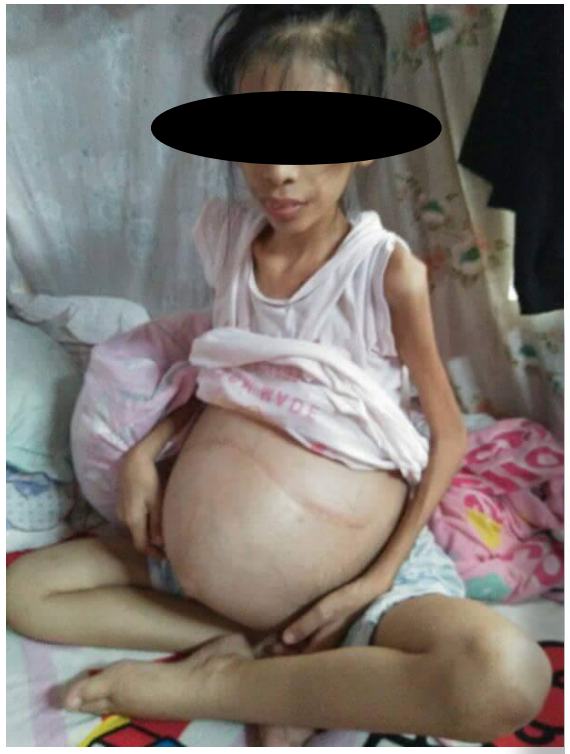
Increase permeability of drug

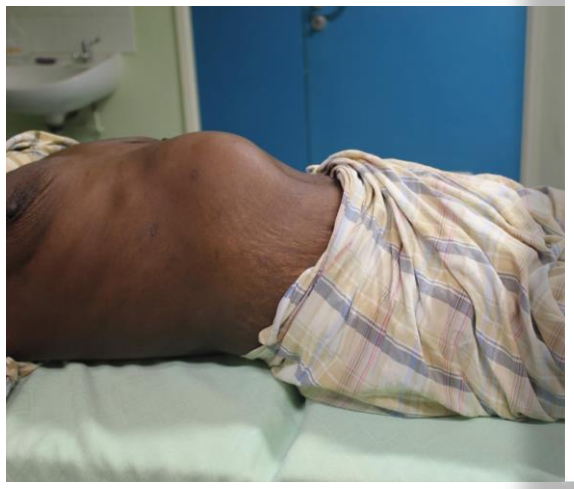
Overcome blood-brain-barrier/ Blood-tumor-barrier

Use of carrier molecules/vehicle

Briolay T, Petithomme T, Fouet M, Nguyen-Pham N, Blanquart C, Boisgerault N. Delivery of cancer therapies by synthetic and bio-inspired nanovectors. Mol Cancer. 2021 Mar 24;20(1):55. doi: 10.1186/s12943-021-01346-2. PMID: 33761944; PMCID: PMC7987750.

The Battle is far from over





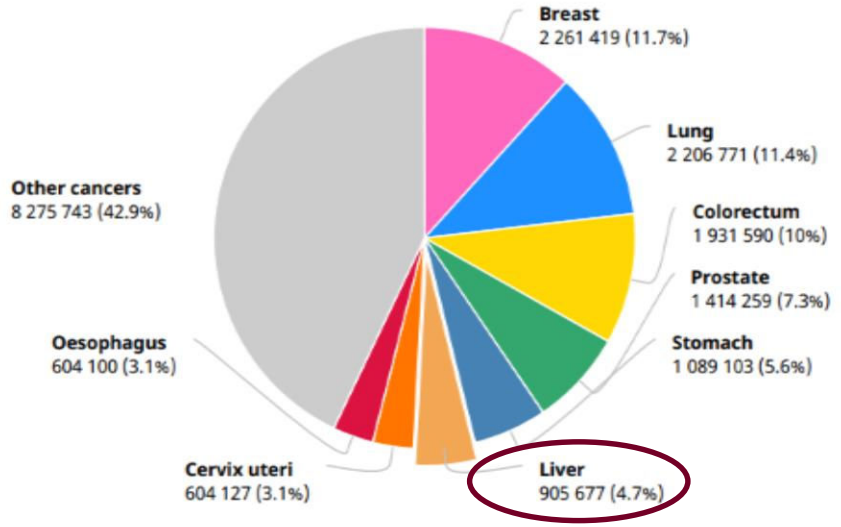
International Agency for Research on Cancer
World Health Organization

Liver

Source: Globocan 2020

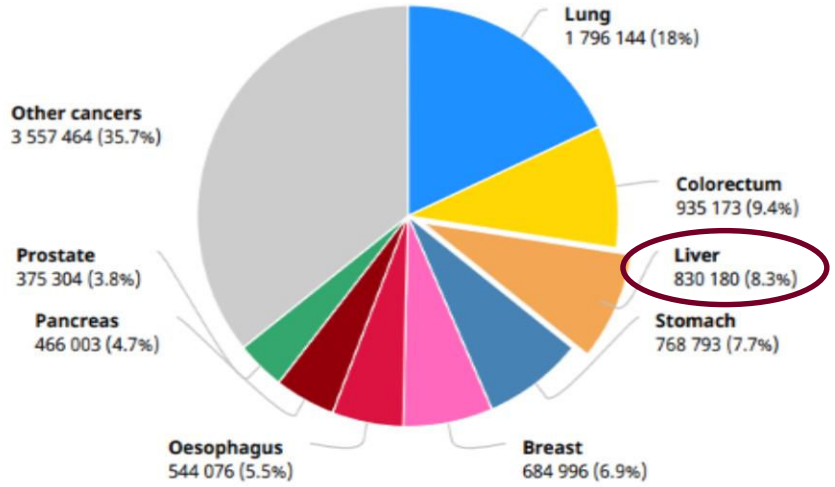
GCO

Number of new cases in 2020, both sexes, all ages



Total: 19 292 789 cases

Number of deaths in 2020, both sexes, all ages



Total: 9 958 133 deaths

https://gogetfunding.com/joana-luna-ortiz-stage-4-liver-cancer/

https://gco.iarc.fr/today/data/factsheets/cancers/11-Liver-fact-sheet.pdf

ARE YOU .....

https://www.soundrosestudio.com/ready-for-battle

Thank You

Questions??