



ΚΑΤ' ΕΠΙΛΟΓΗ ΜΑΘΗΜΑ ΑΚΤΙΝΟΒΙΟΛΟΓΙΑ – ΑΚΤΙΝΟΘΕΡΑΠΕΙΑ
ΔΙΑΔΙΚΤΥΑΚΑ ΜΑΘΗΜΑΤΑ ΕΑΡΙΝΟΥ ΕΞΑΜΗΝΟΥ 2021

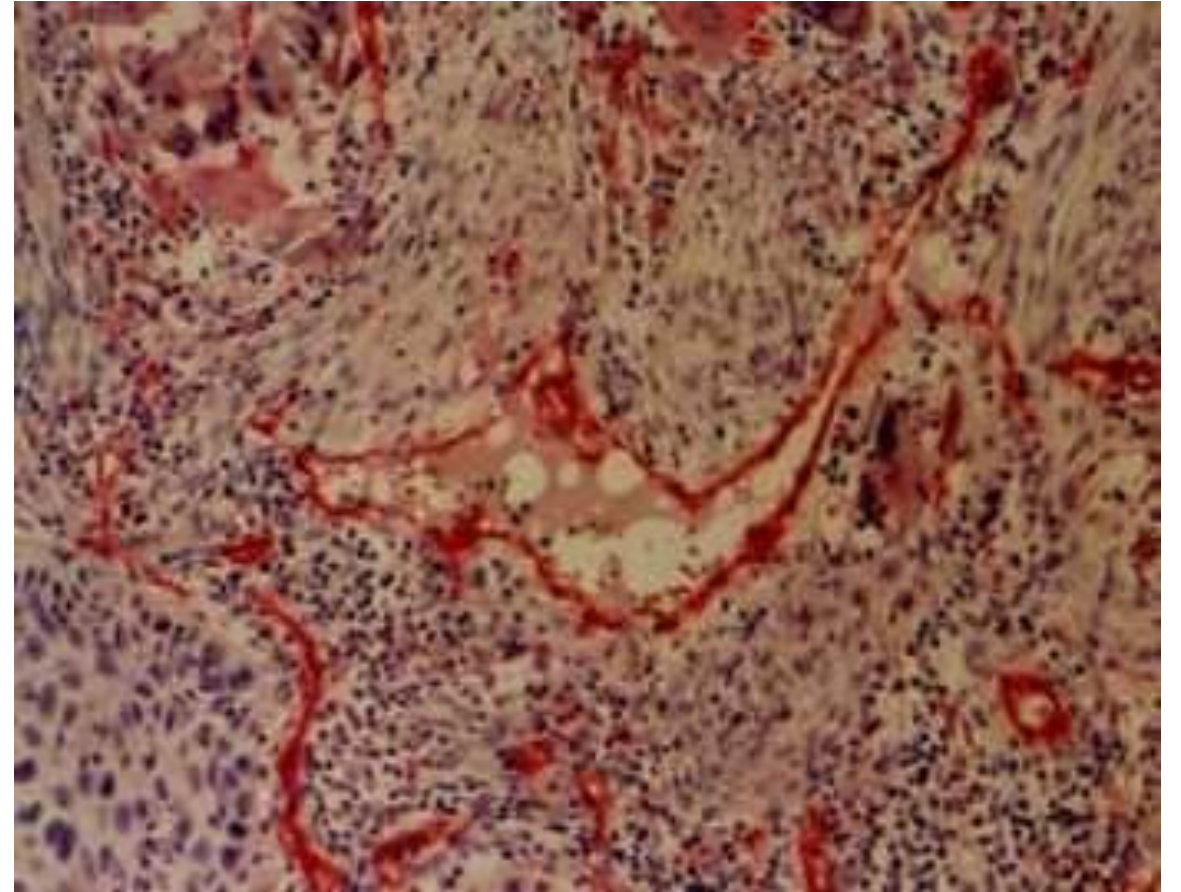
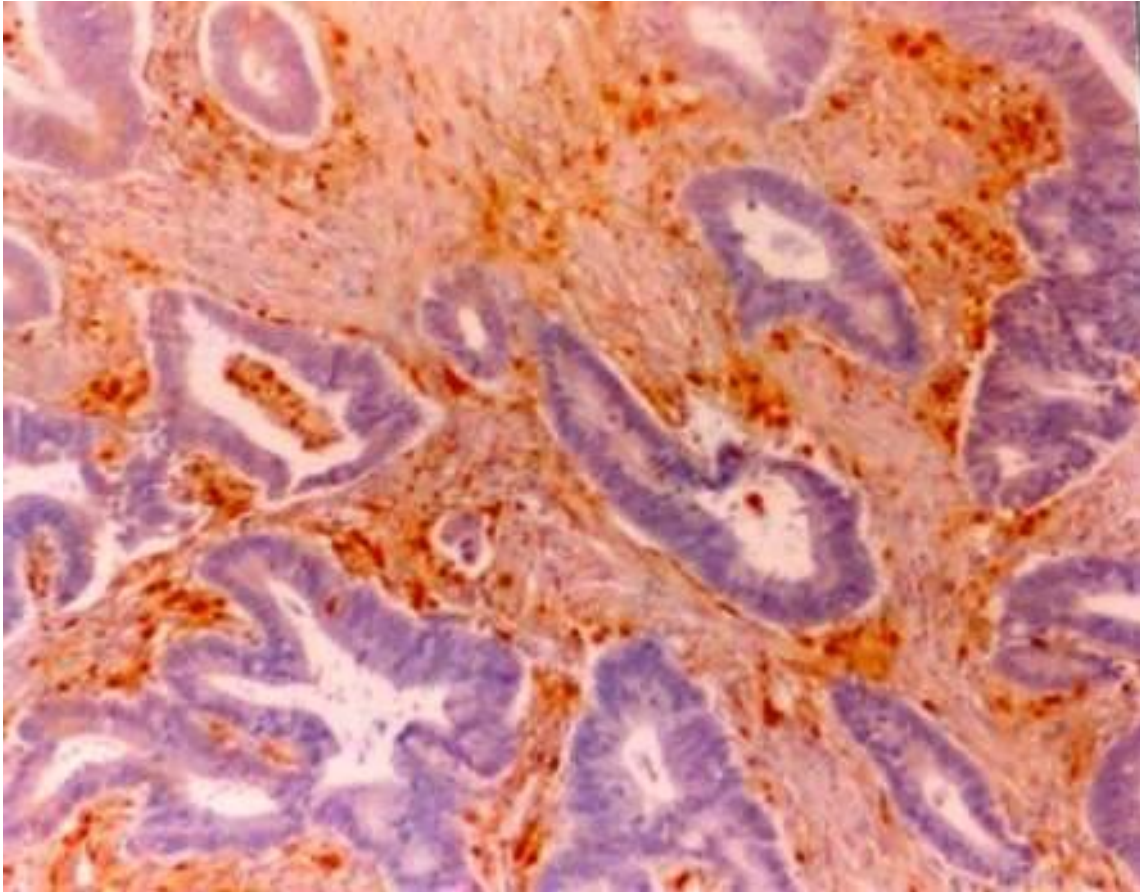
Υπεύθυνος: Καθηγητής Δημήτριος Καρδαμάκης

ΑΓΓΕΙΟΓΕΝΕΣΗ



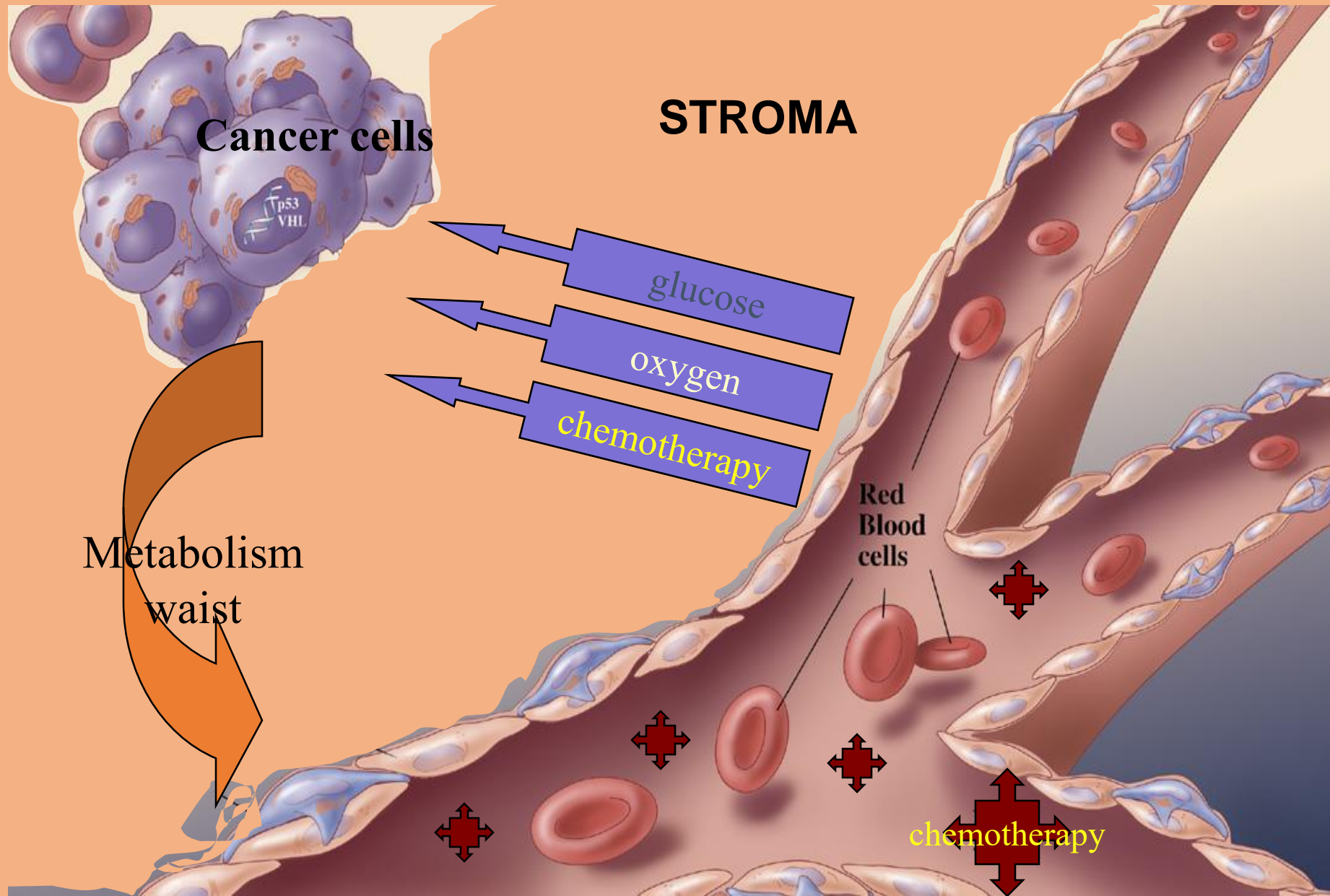
Μιχαήλ Ι. Κουκουράκης
Καθηγητής
Ακτινοθεραπευτικής - Ογκολογίας
Δημοκρίτειο Πανεπιστήμιο Θράκης

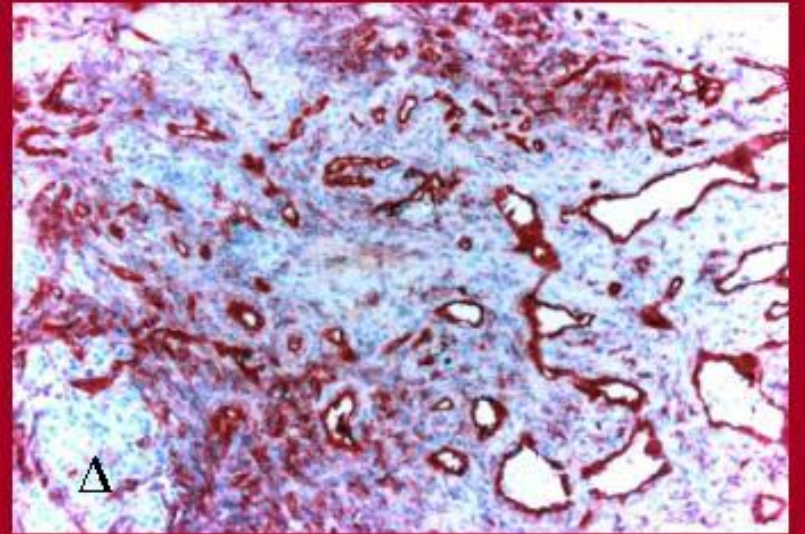
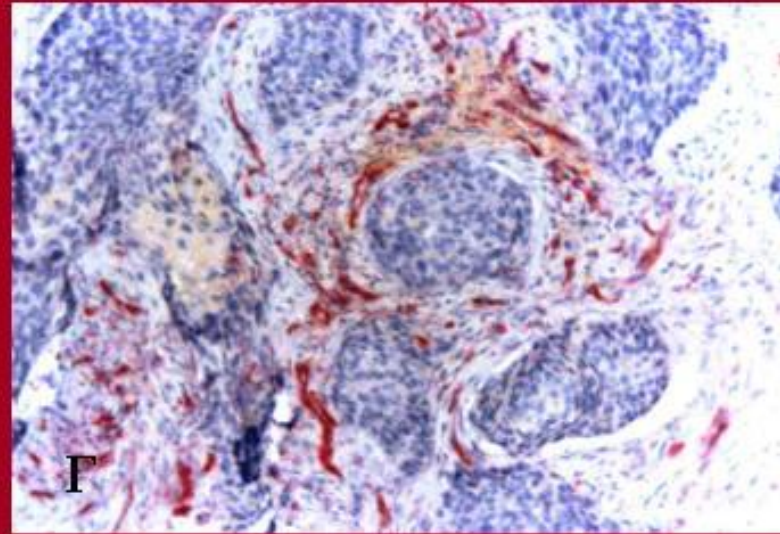
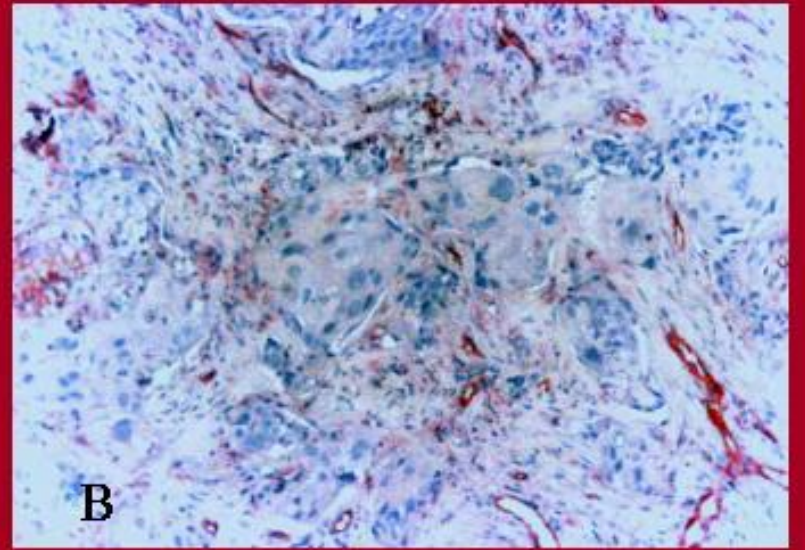
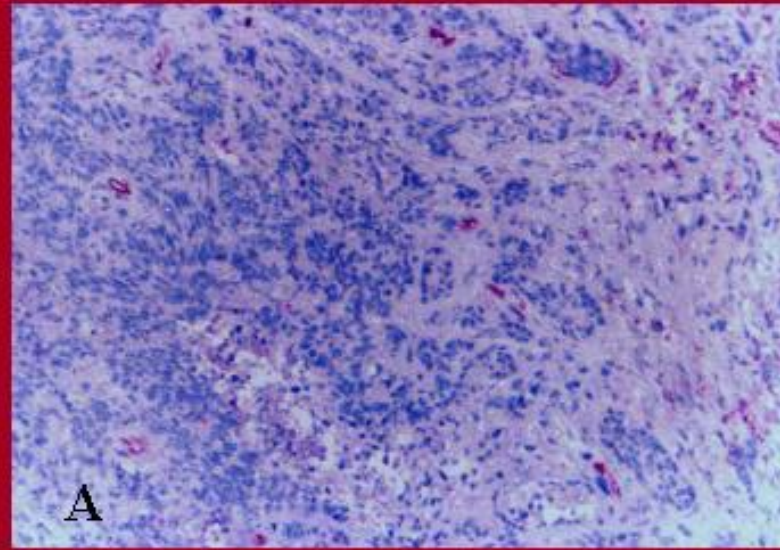
Ο ΟΓΚΟΣ ΔΕΝ ΕΙΝΑΙ ΜΑΖΑ ΑΠΌ ΚΑΡΚΙΝΙΚΑ ΚΥΤΤΑΡΑ !



ΚΑΡΚΙΝΙΚΑ ΚΥΤΤΑΡΑ + ΣΤΡΩΜΑ (ΙΝΟΒΛΑΣΤΕΣ – ΑΓΓΕΙΑ – ΑΝΟΣΟΛΟΓΙΚΑ ΚΥΤΤΑΡΑ)

ΤΟ ΑΓΓΕΙΑΚΟ ΔΙΚΤΥΟ ΤΟΥ ΟΓΚΟΥ ΚΑΘΟΡΙΖΕΙ ΤΗΝ ΑΙΜΑΤΙΚΗ ΡΟΗ ΠΡΟΣ ΤΟΝ ΟΓΚΟ

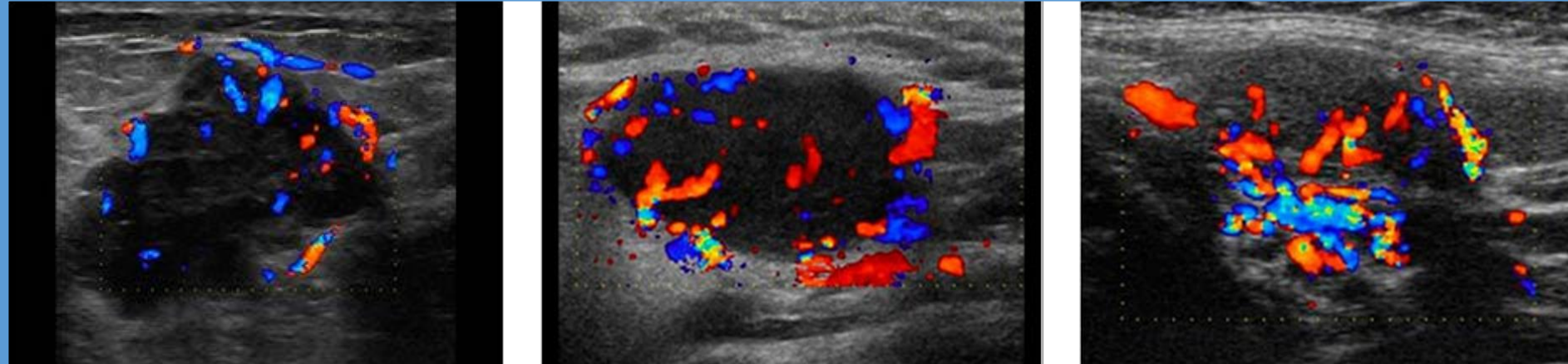




Giatromanolaki A, Koukourakis MI et al.
Angiogenesis vs. response after
combined chemoradiotherapy of
squamous cell head and neck cancer.
Int J Cancer. 1999 Mar 15;80(6):810-7

Head-Neck Squamous Cell Cancer

ΤΟ ΑΓΓΕΙΑΚΟ ΔΙΚΤΥΟ ΤΟΥ ΟΓΚΟΥ ΚΑΘΟΡΙΖΕΙ ΤΗΝ ΔΙΑΘΕΣΙΜΟΤΗΤΑ ΤΗΣ ΧΗΜΕΙΟΘΕΡΑΠΕΙΑΣ

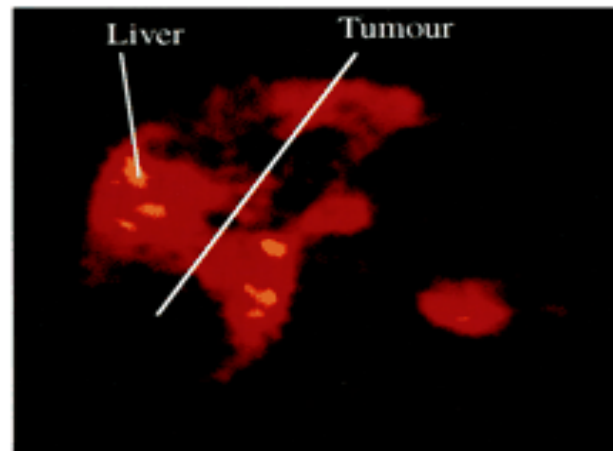


Color-Doppler
Ultrasonography
of
Breast Cancer

Aboagye EO, Saleem A, Cunningham VJ,
Osman S, Price PM.

Extraction of 5-fluorouracil by tumor and
liver: a noninvasive positron emission
tomography study of patients with
gastrointestinal cancer.

Cancer Res. 2001 Jul 1;61(13):4937-41.

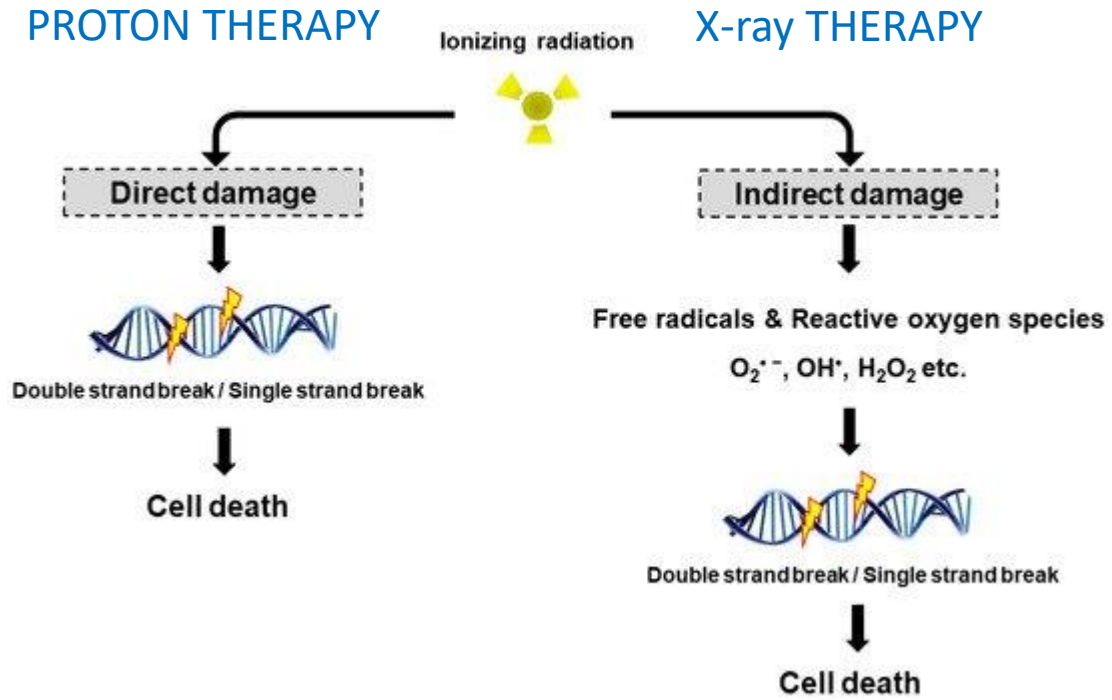


(a)

This study provides evidence that
the cytotoxicity of 5-FU in patients with
gastrointestinal cancer
could be compromised by its intrinsically
low uptake by tumors,
as well as decreased systemic
availability through hepatic catabolism.

(b)

ΤΟ ΑΓΓΕΙΑΚΟ ΔΙΚΤΥΟ ΤΟΥ ΟΓΚΟΥ ΚΑΘΟΡΙΖΕΙ ΤΗΝ ΔΙΑΘΕΣΙΜΟΤΗΤΑ ΤΟΥ ΟΞΥΓΟΝΟΥ

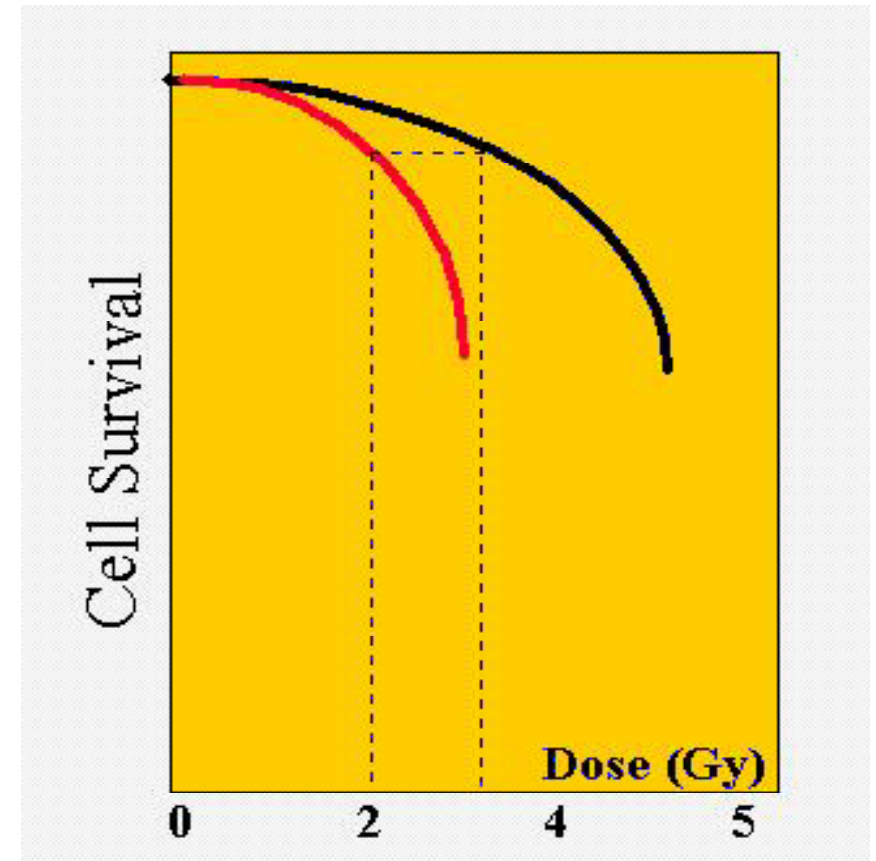


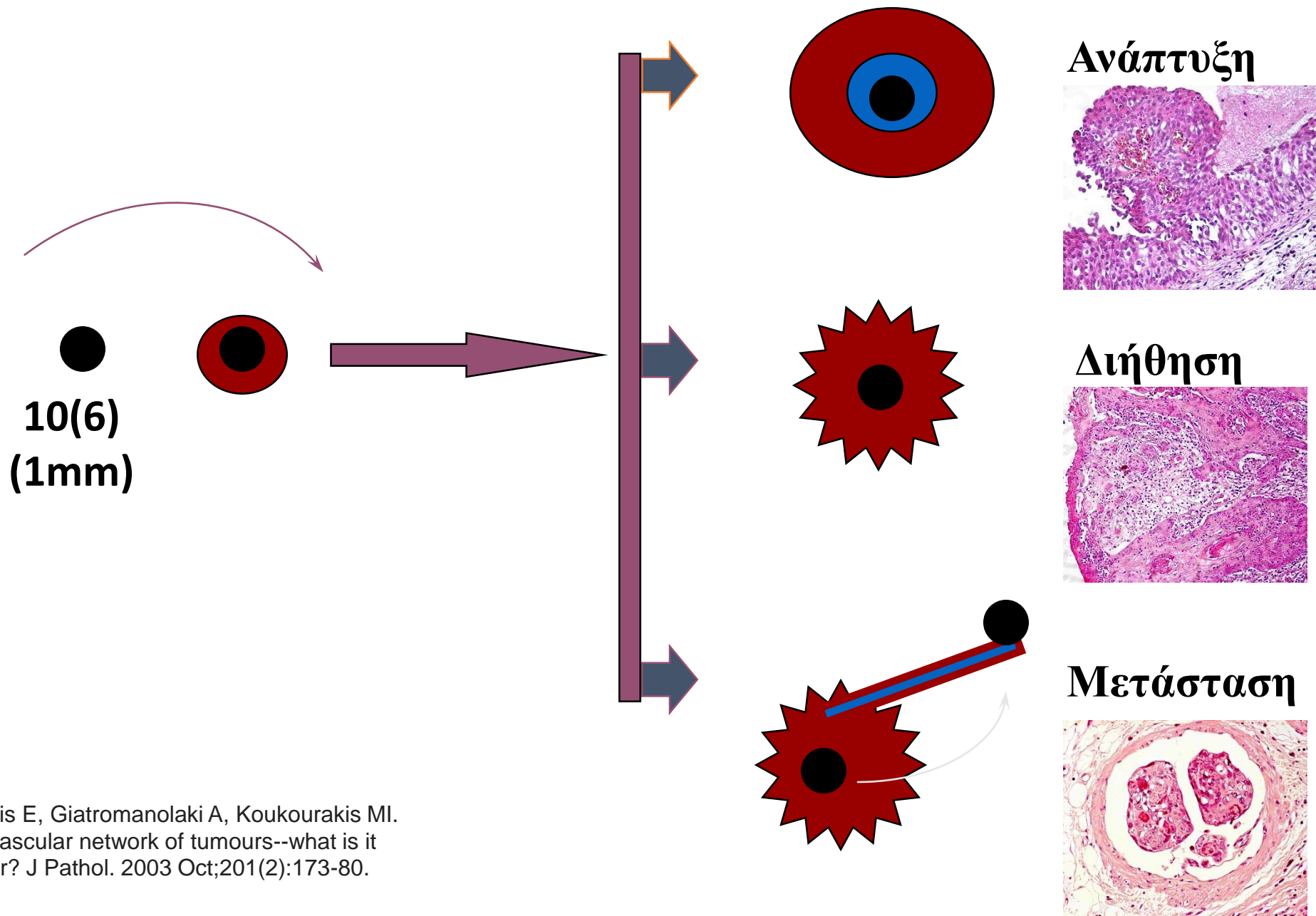
200 εκ. ευρώ



2 εκ. ευρώ

Oxygen Effect in Radiotherapy





Sivridis E, Giatromanolaki A, Koukourakis MI.
 The vascular network of tumours--what is it
 not for? J Pathol. 2003 Oct;201(2):173-80.

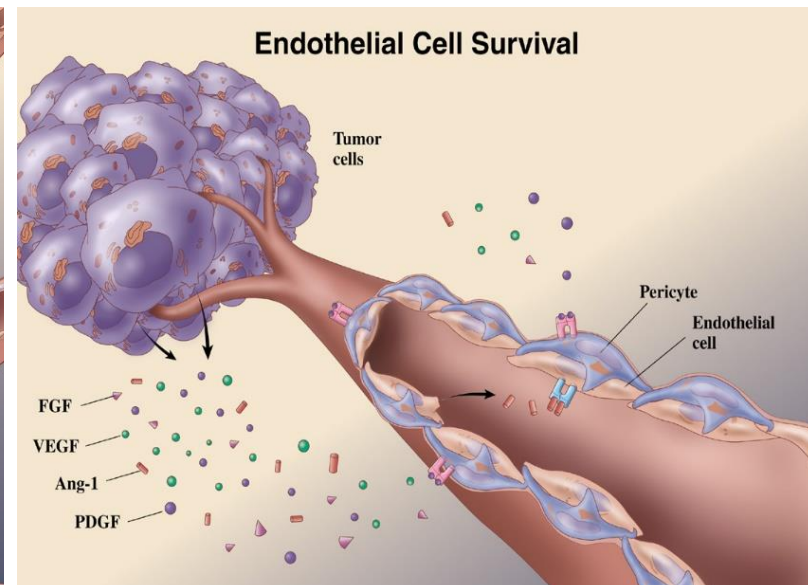
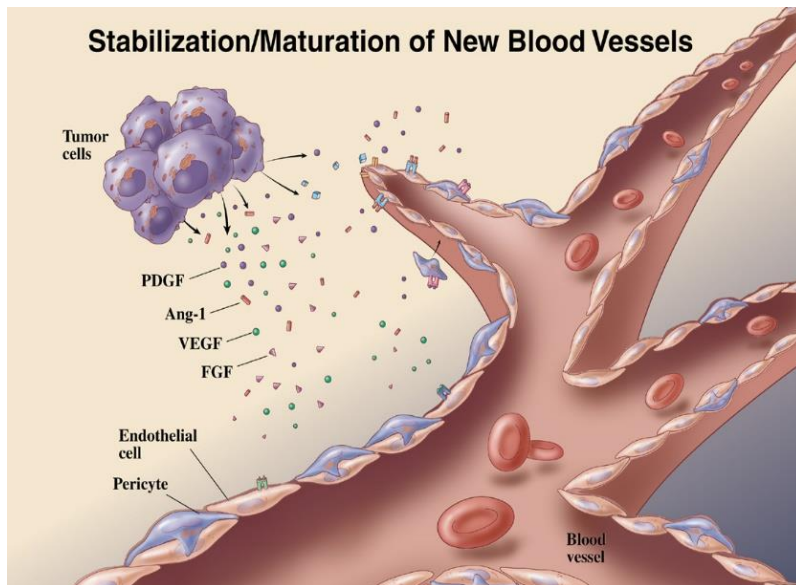
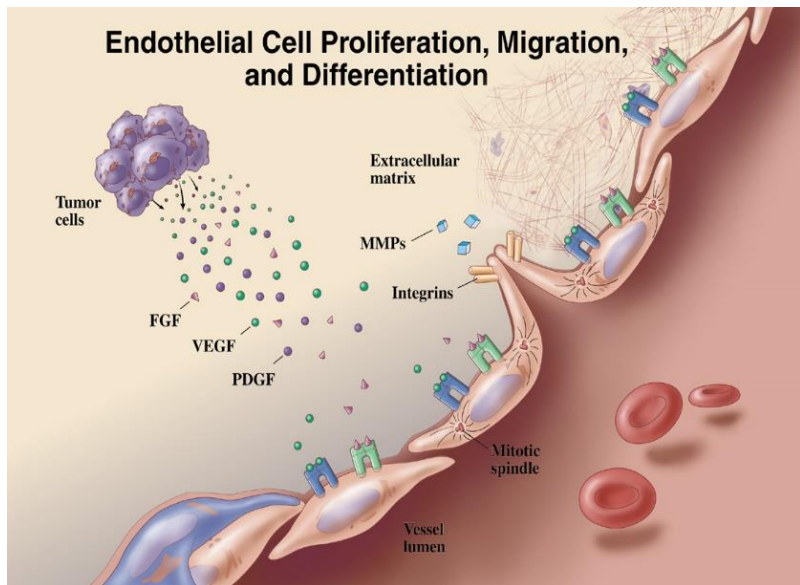
Κάθε όγκος αναπτύσσει το δικό του αγγειακό δίκτυο επιδρώντας πάνω στα ενδοθηλιακά κύτταρα
Γειτονικών φυσιολογικών αγγείων μέσω έκκρισης ΑΓΓΕΙΟΓΕΝΩΝ ΠΑΡΑΓΟΝΤΩΝ

Angiogenic Growth Factors:

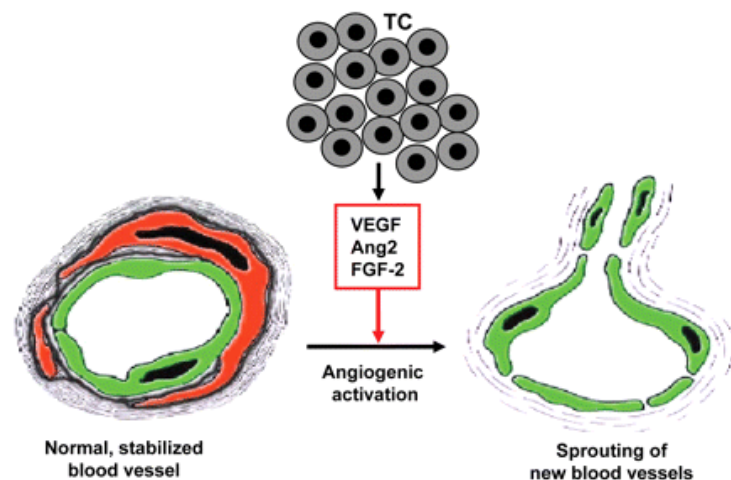
- VEGF (Vascular Endothelial Growth Factor)
- bFGF (basic Fibroblast Growth Factor)
- HGF (Hepatocyte Growth factor)
- PDGF (Platelet Derived Growth Factor)
- Angiopoietin 1-4

Angiogenic Growth factor Receptors:

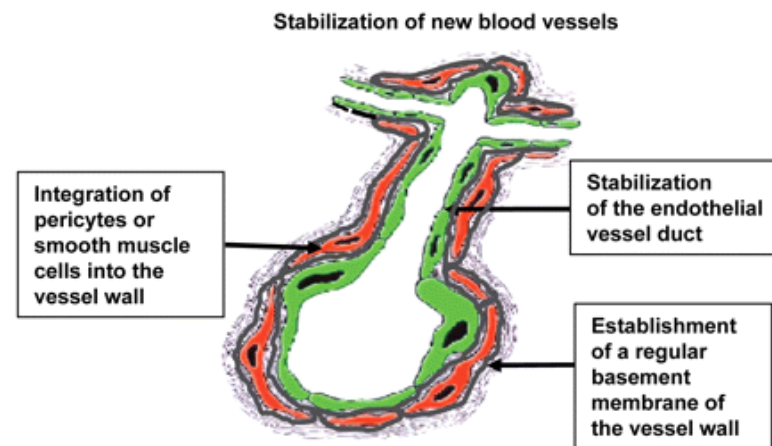
- FLK1, KDR
- FGF-R
- c-Met receptors
- PDGF-R
- Tie-1 Tie-2 receptors



Αγγειακή Γένεση

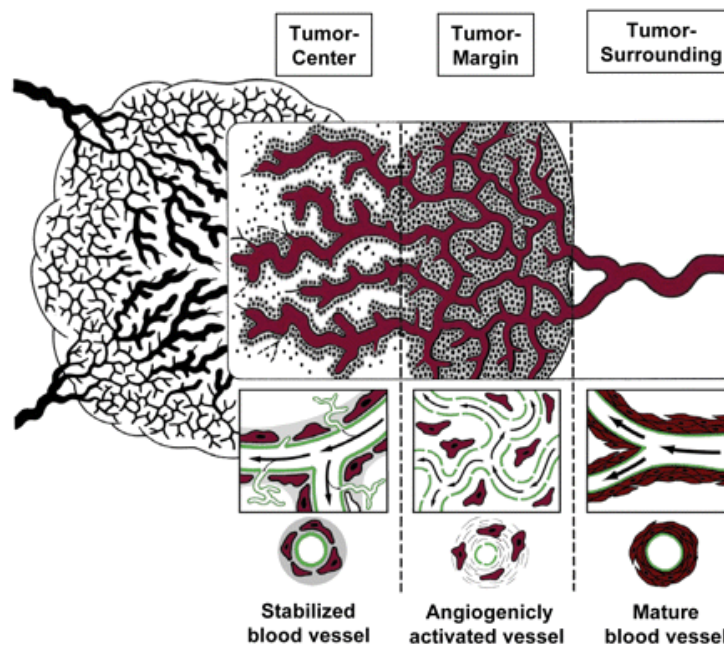


Αγγειακή Ωρίμανση



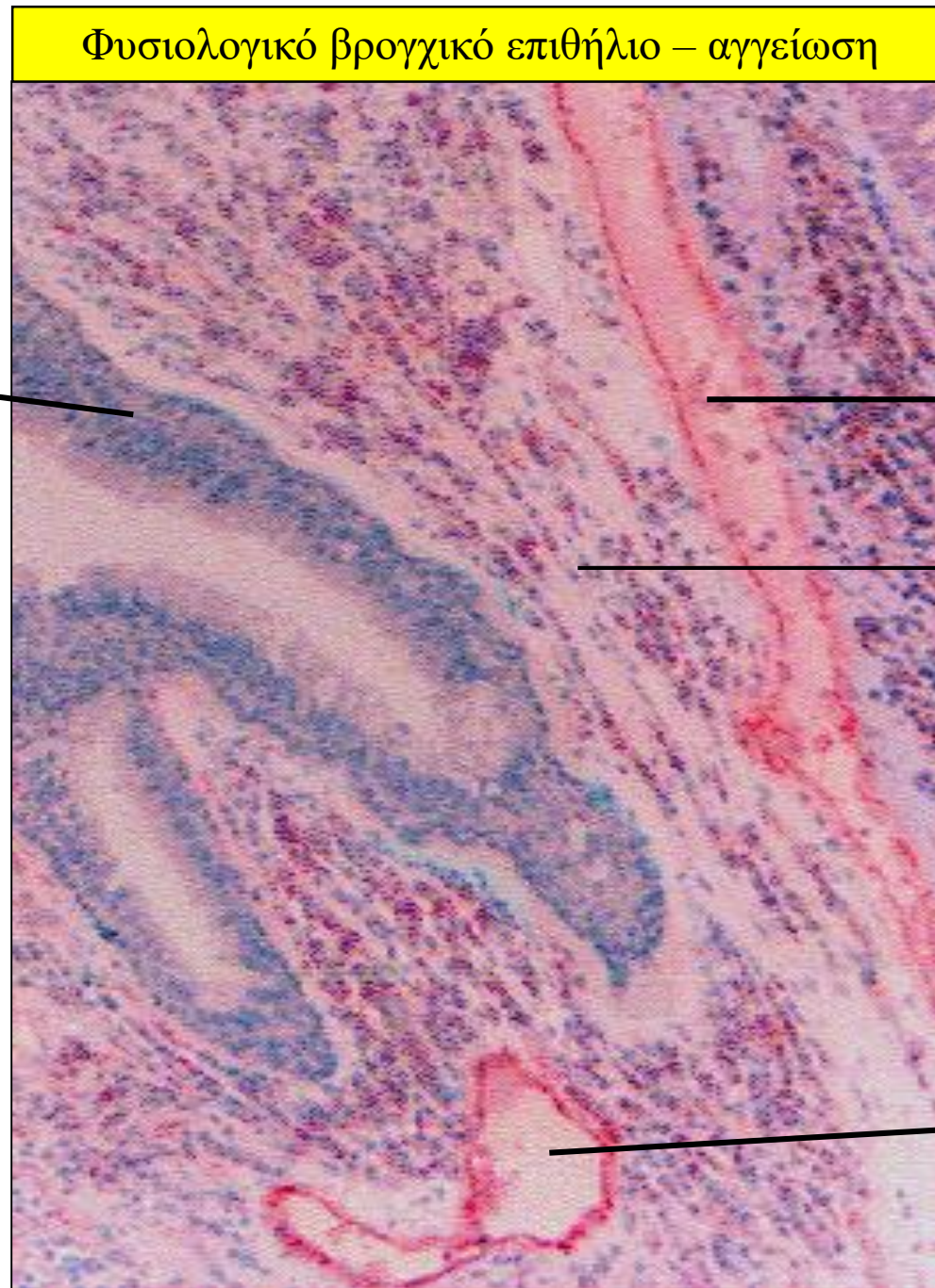
ΡΟΗ ΑΙΜΑΤΟΣ ΕΝΤΟΣ ΤΟΥ ΟΓΚΟΥ

- A. Αγγειακή πυκνότητα
- B. Αγγειακή ωρίμανση
- Γ. Αγγειακή αρχιτεκτονική



Tilki D, Seitz M, Singer BB, Irmak S, Stief CG, Reich O, Ergün S. Molecular imaging of tumor blood vessels in prostate cancer. *Anticancer Res.* 2009 May;29(5):1823-9.

Φυσιολογικό βρογχικό επιθήλιο – αγγείωση



Βρογχικό
επιθήλιο



Αγγείο



Συνδετικός
Ιστός



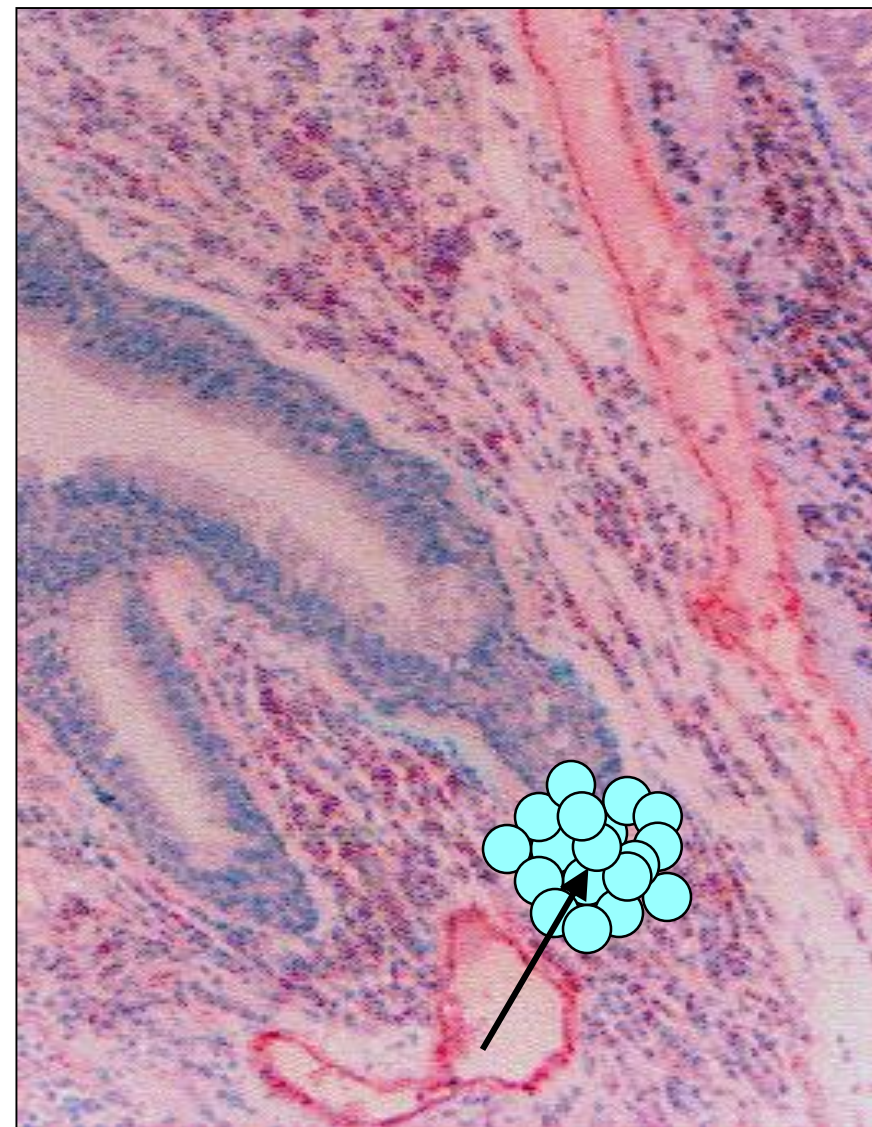
Αγγείο



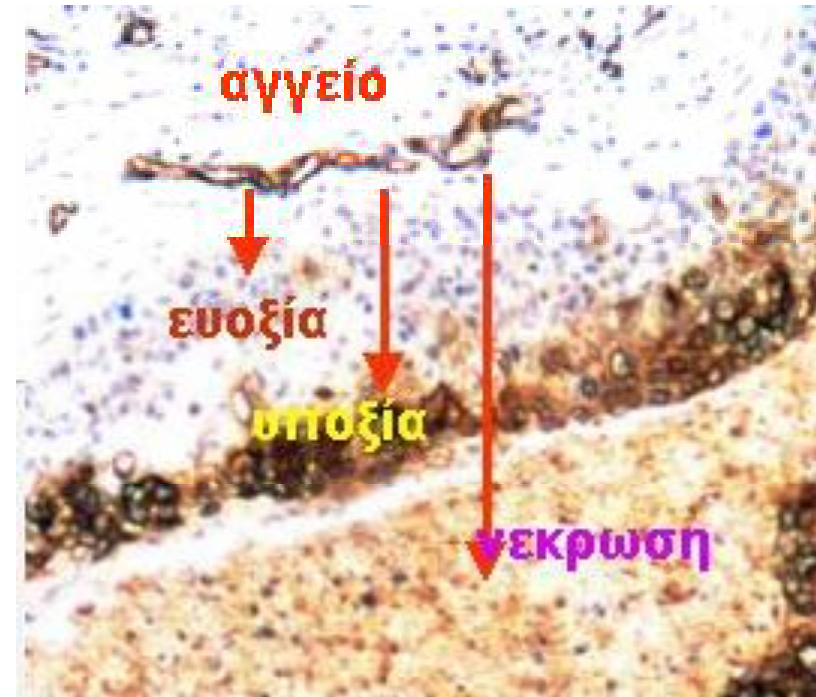
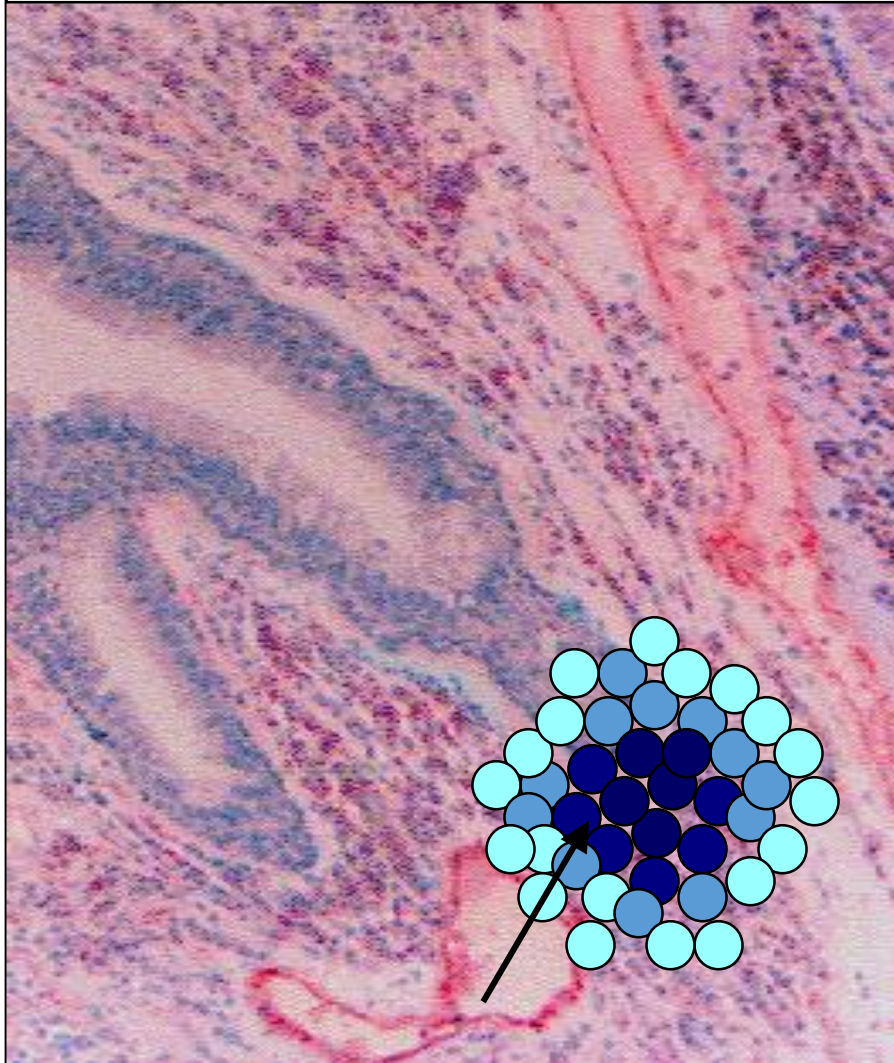
Εμφάνιση ενός καρκινικού κυττάρου



Μάζα καρκινικών κυττάρων <math>< 2\text{mm}</math>

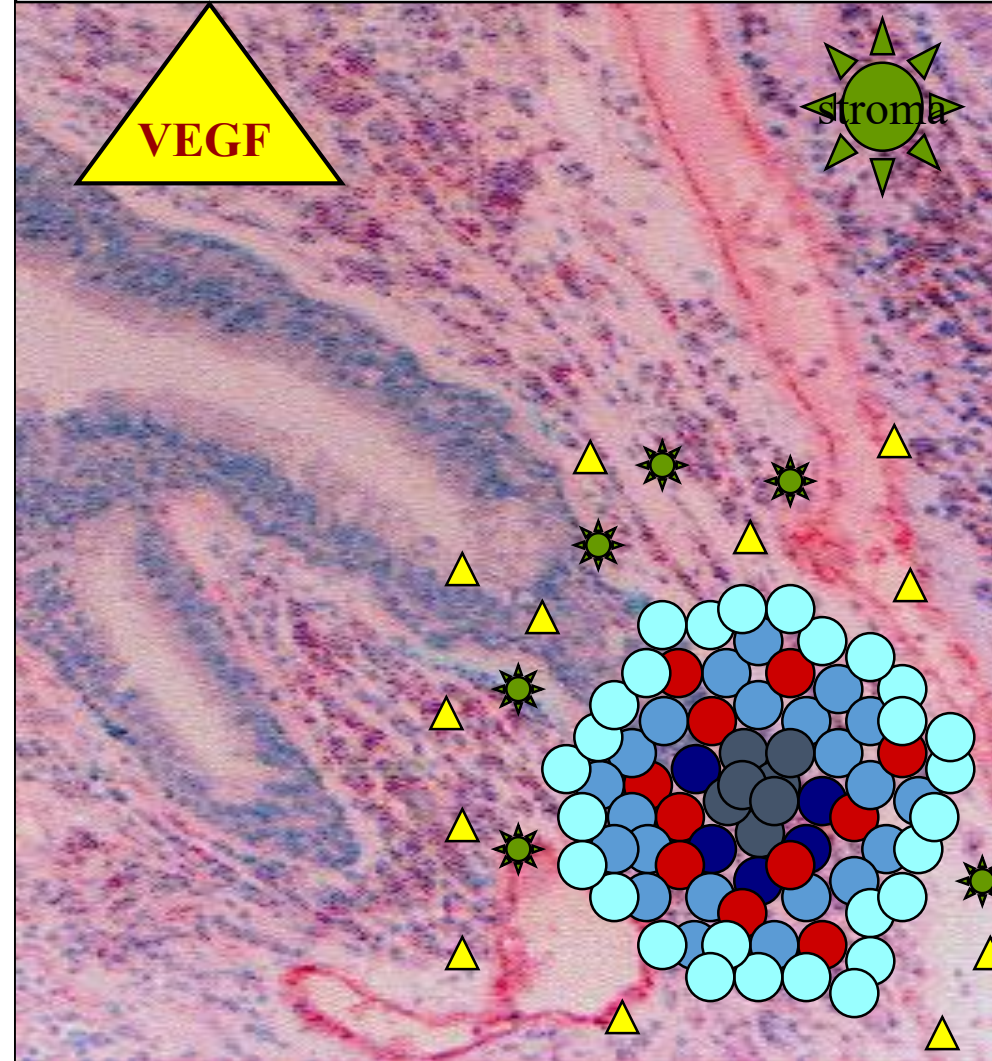


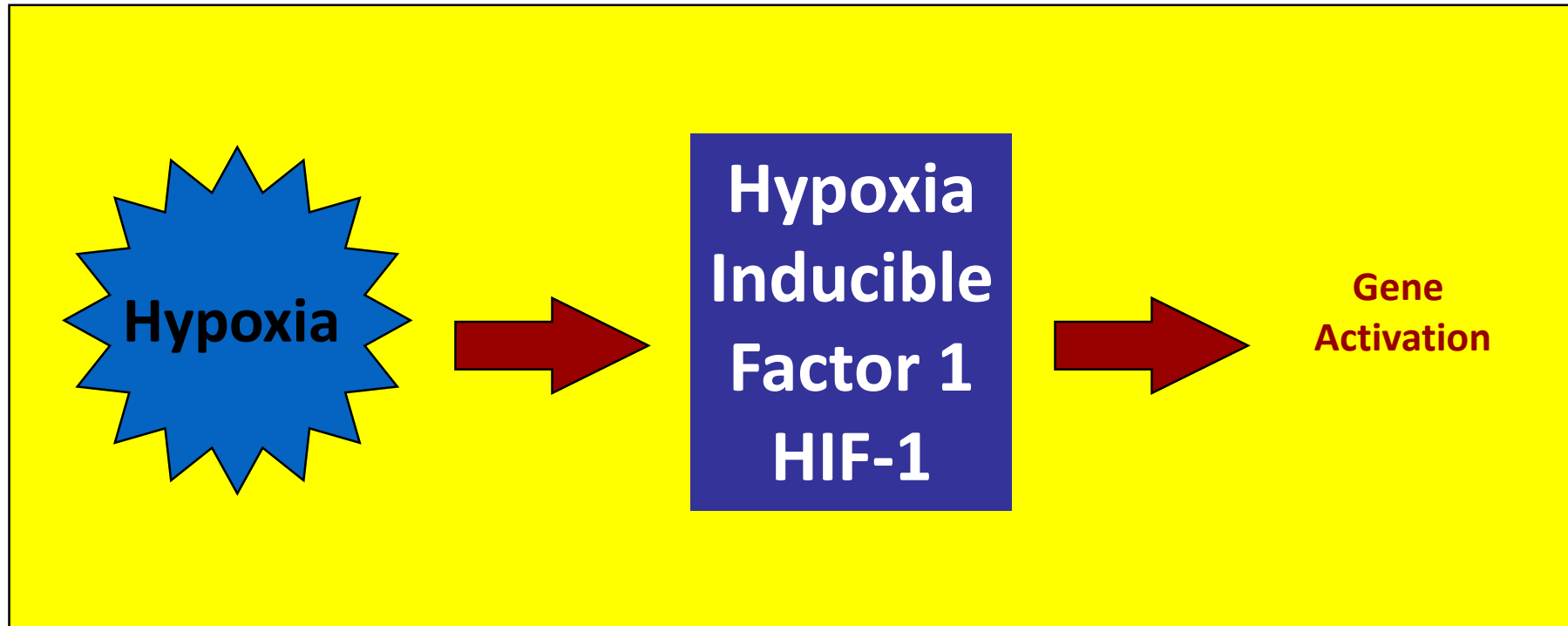
Μάζα καρκινικών κυττάρων >2mm
Εμφάνιση κεντρικής υποξίας
Εμφάνιση υποξικού φαινότυπου



Ανοσοϊστοχημική έκφραση
Καρβονικής Ανυδράσης 9

Εμφάνιση του Υποξικού Φαινότυπου.
Παραγωγή 'growth factors' που προάγουν
την αγγειογένεση και στρωματογένεση





HIF-1 είναι ένας μεταγραφικός παράγοντας η συγκέντρωση του οποίου αυξάνεται σε συνθήκες υποξίας (Sementza and Wang 1991)

Normoxia

Hypoxia

Sensor
Heme flavo-oxido
reductase

Prolyl-hydroxylases

HIF-1 α degradation

HIF-1 stabilisation

α

α

β

Nucleus
Target Gene

CELL

Erythropoiesis:

Erythropoietin (Epo)

Angiogenesis:

VEGF, PD-ECGF

Angiogenesis Receptors:

Tie-1, Flk-1

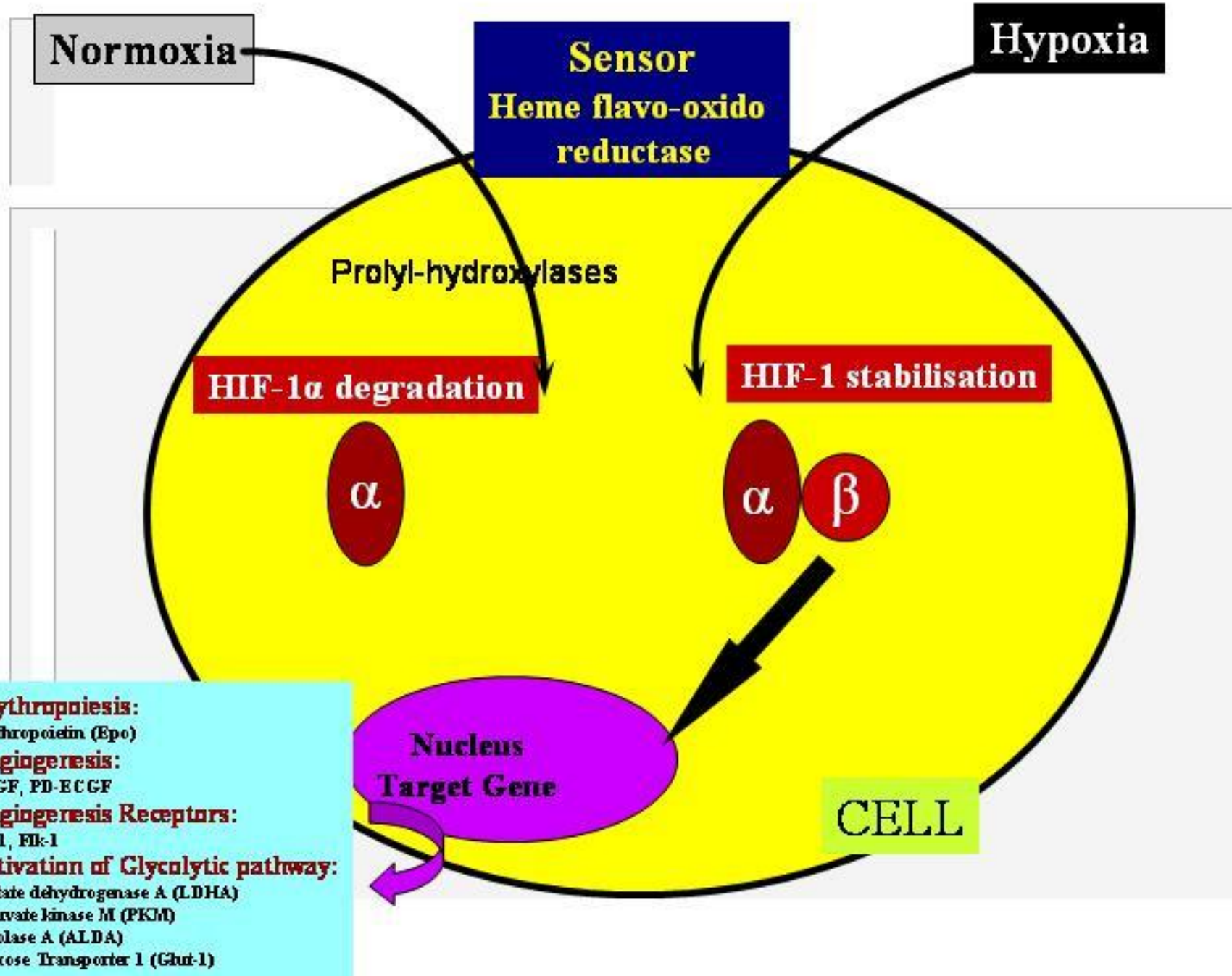
Activation of Glycolytic pathway:

Lactate dehydrogenase A (LDHA)

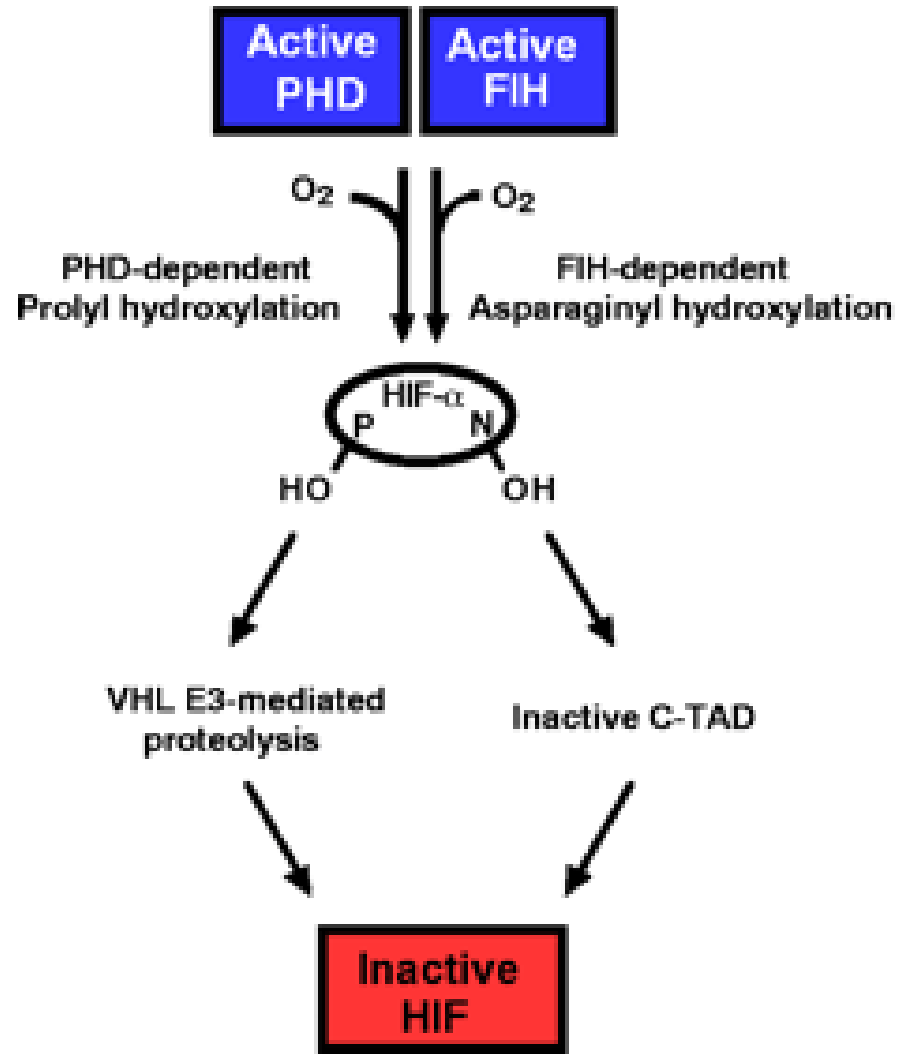
Pyruvate kinase M (PKM)

Aldolase A (ALDA)

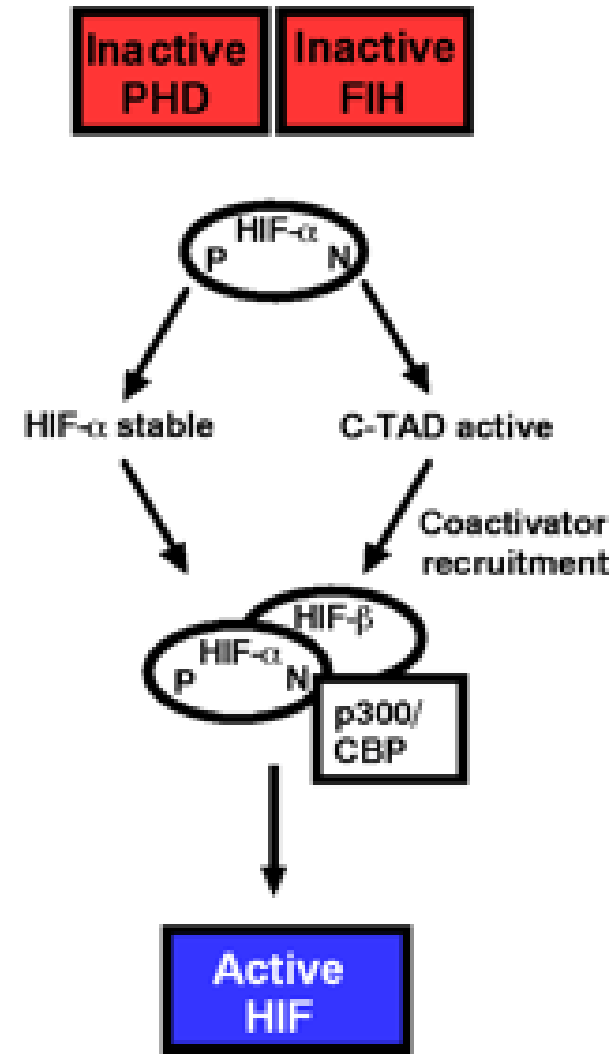
Glucose Transporter 1 (Glut-1)



Normoxia



Hypoxia



THE NOBEL PRIZE IN PHYSIOLOGY OR MEDICINE 2019

Illustrations: Niklas Elmehed



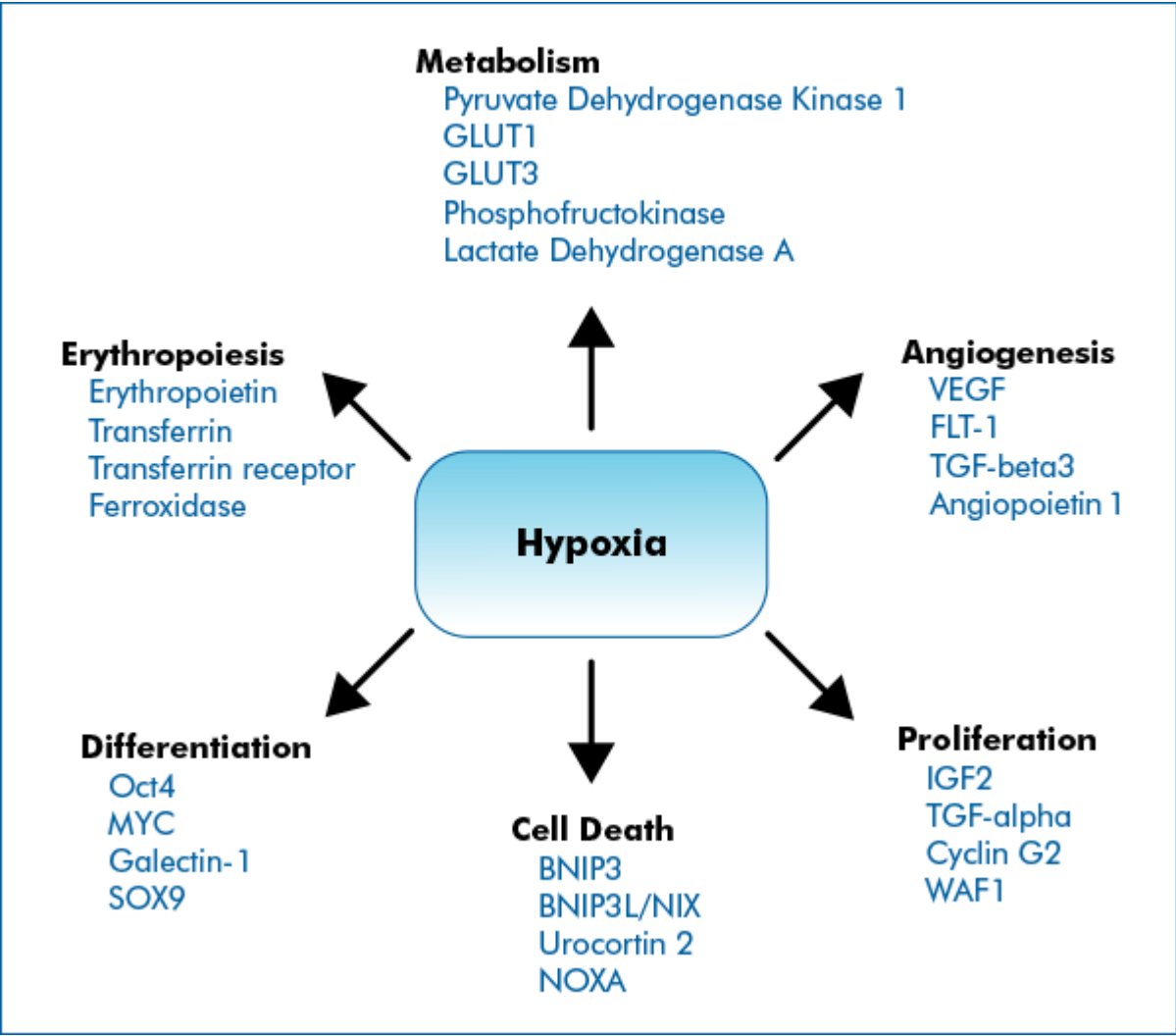
William G.
Kaelin Jr.

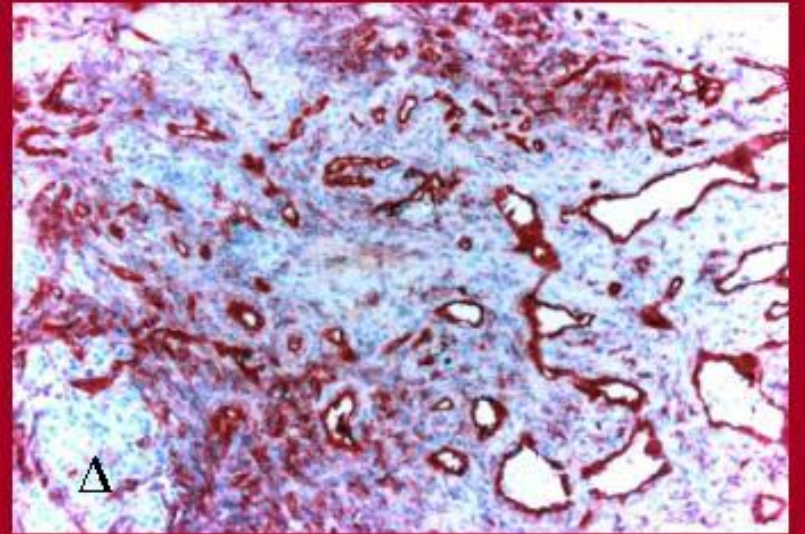
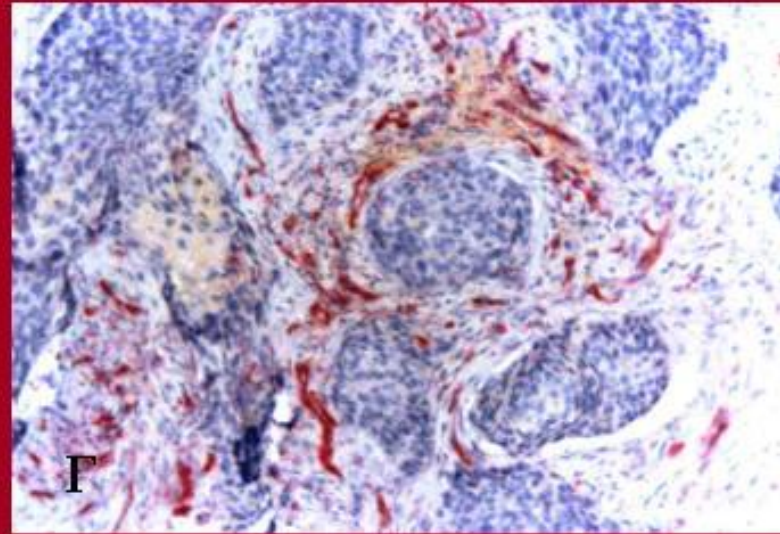
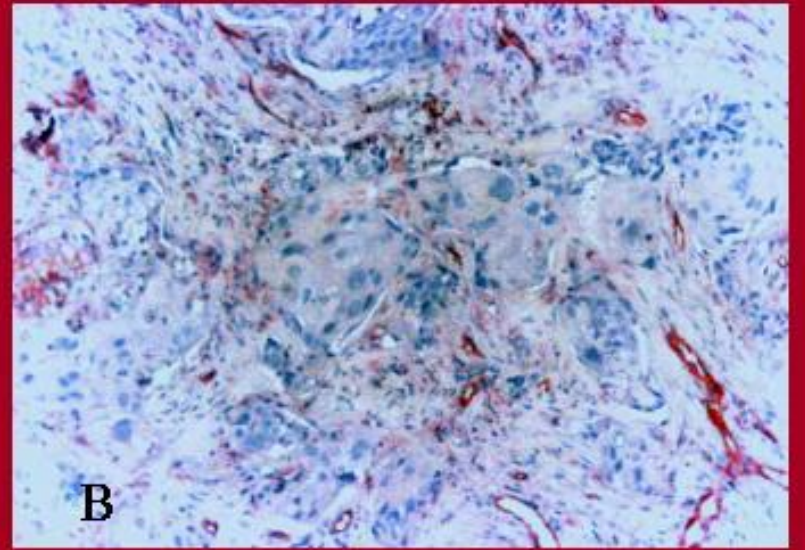
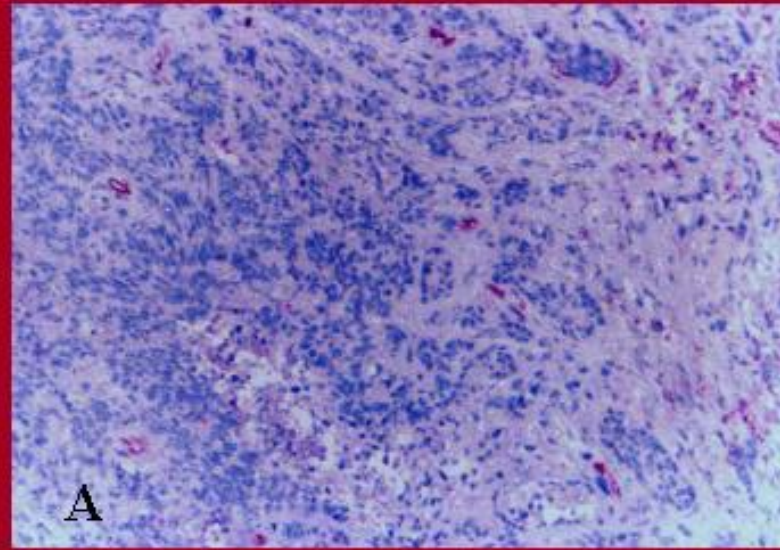
Sir Peter J.
Ratcliffe

Gregg L.
Semenza

“for their discoveries of how cells sense
and adapt to oxygen availability”

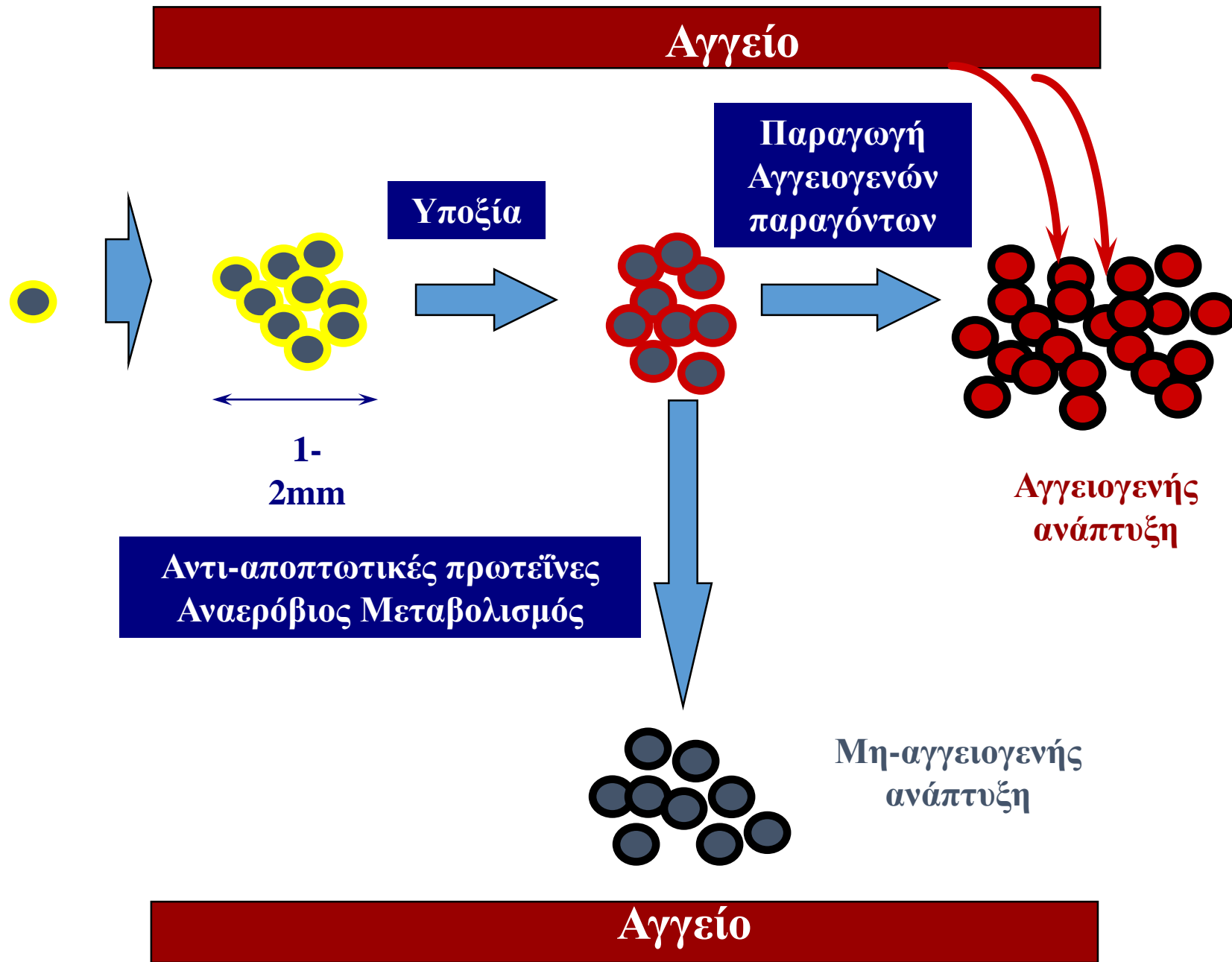
THE NOBEL ASSEMBLY AT KAROLINSKA INSTITUTET





Giatromanolaki A, Koukourakis MI et al.
Angiogenesis vs. response after
combined chemoradiotherapy of
squamous cell head and neck cancer.
Int J Cancer. 1999 Mar 15;80(6):810-7

Head-Neck Squamous Cell Cancer



Cancer cells prefer to transform glucose to lactate for energy acquisition, even in well oxygenated conditions



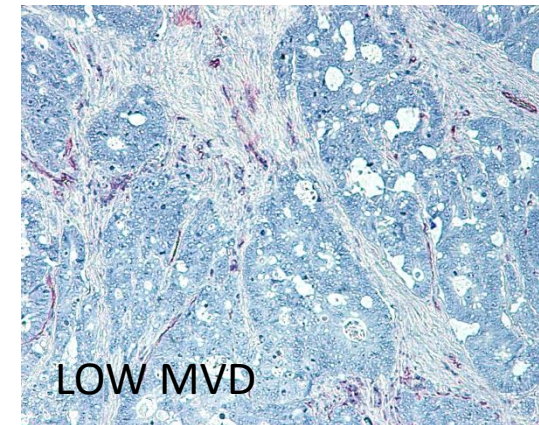
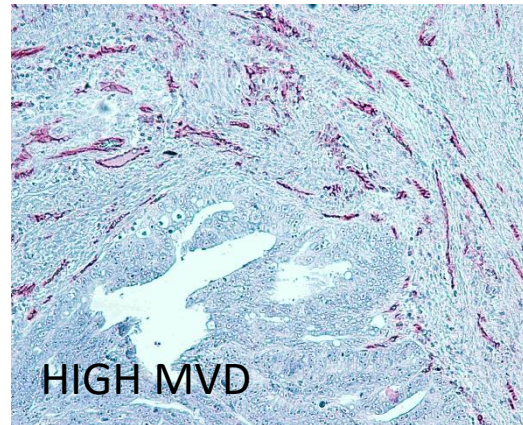
WARBURG EFFECT
Aerobic Glycolysis

Otto Warburg
Nobel Prize 1931

ΕΚΤΙΜΗ ΤΗΣ ΑΓΓΕΙΟΓΕΝΕΣΗΣ ΣΤΟΥΣ ΟΓΚΟΥΣ

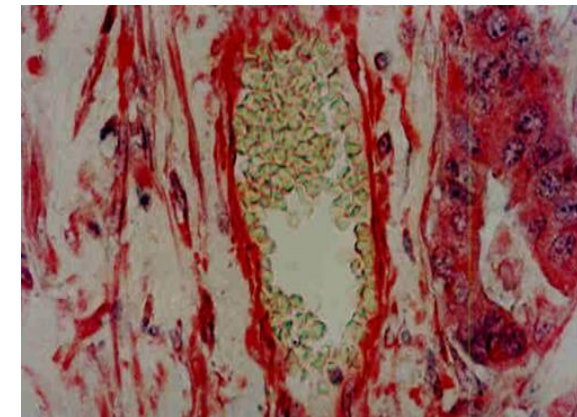
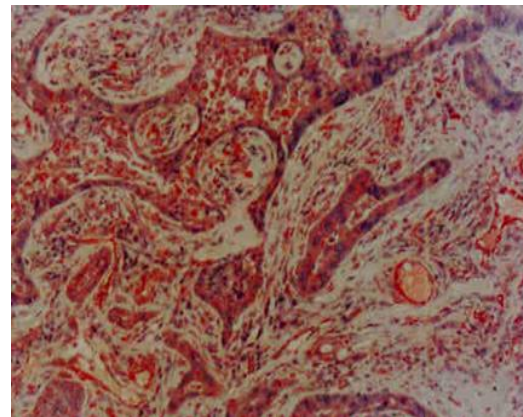
ΕΚΤΙΜΗ ΤΗΣ ΑΓΓΕΙΟΓΕΝΕΣΗΣ ΣΤΟΥΣ ΟΓΚΟΥΣ

Ανοσοϊστοχημική χρώση για CD31
(Μικροαγγειακή πυκνότητα)



Giatriomanolaki A, Sivridis E, Minopoulos G, Polychronidis A, Manolas C, Simopoulos C, Koukourakis MI. Differential assessment of vascular survival ability and tumor angiogenic activity in colorectal cancer. Clin Cancer Res 2002; 8:1185-1191

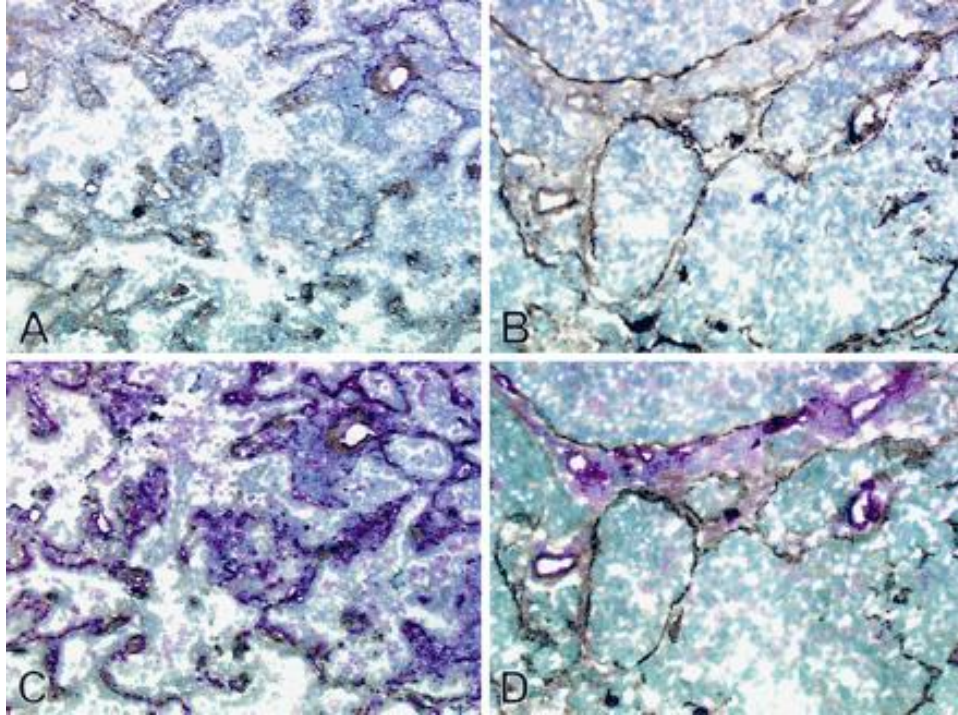
Ανοσοϊστοχημική χρώση για
Ανίχνευση αγγειογενών παραγόντων
(πχ. VEGF ή VEGF-receptors)



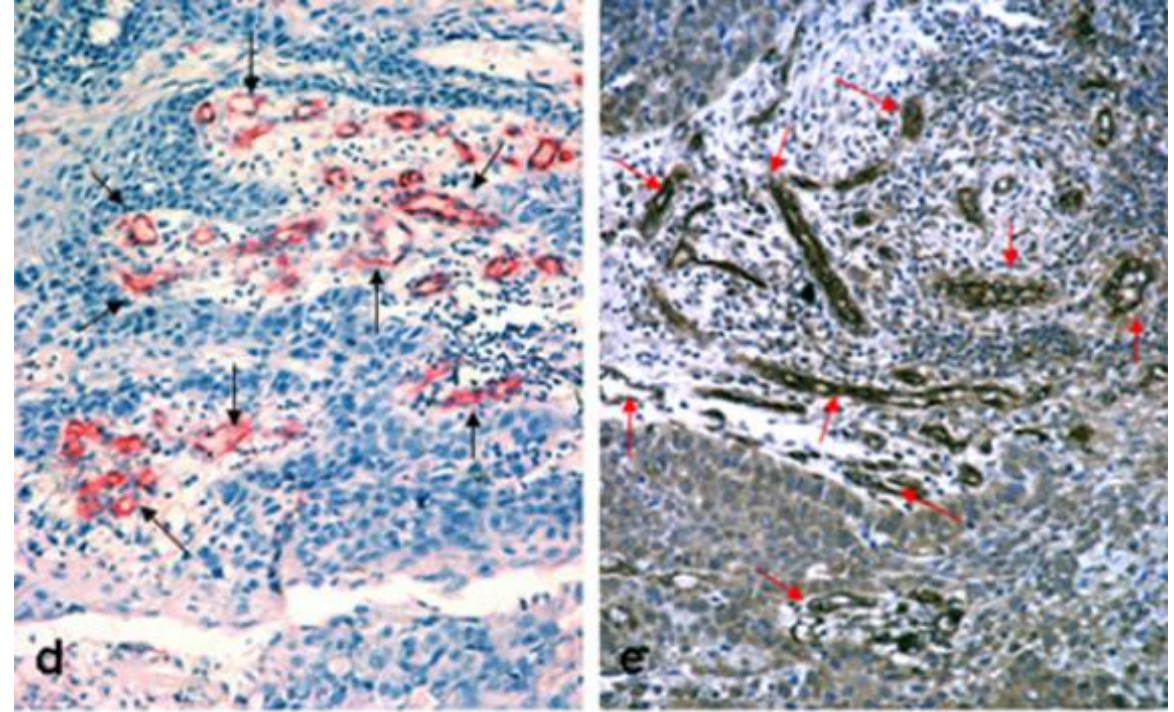
Koukourakis MI, Giatriomanolaki A, Thorpe PE, Brekken RA, Sivridis E, Kakolyris S, Georgoulas V, Gatter KC, Harris AL. Vascular endothelial growth factor/KDR activated microvessel density versus CD31 standard microvessel density in non-small cell lung cancer. Cancer Res. 2000 Jun 1;60(11):3088-95.

ΕΚΤΙΜΗ ΤΗΣ ΑΓΓΕΙΑΚΗΣ ΩΡΙΜΑΝΣΗΣ ΣΤΟΥΣ ΟΓΚΟΥΣ

Basement membrane components



DLL4 expression



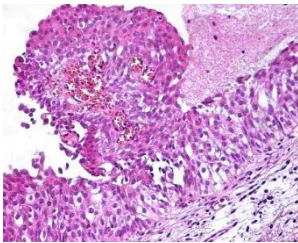
Kakolyris S, Giatromanolaki A, Koukourakis M, Leigh IM, Georgoulas V, Kanavaros P, Sivridis E, Gatter KC, Harris AL. Assessment of vascular maturation in non-small cell lung cancer using a novel basement membrane component, LH39: correlation with p53 and angiogenic factor expression. *Cancer Res.* 1999 Nov 1;59(21):5602-7.

Koukourakis MI, Giatromanolaki A, Sivridis E, Gatter KC, Harris AL. High DLL4 expression in tumour-associated vessels predicts for favorable radiotherapy outcome in locally advanced squamous cell head-neck cancer (HNSCC). *Angiogenesis.* 2013 Apr;16(2):343-51.

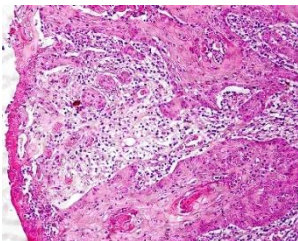
ΕΚΤΙΜΗ ΤΗΣ ΑΓΓΕΙΟΓΕΝΕΣΗΣ / ΩΡΙΜΑΝΣΗΣ ΣΤΟΥΣ ΟΓΚΟΥΣ

Εκτίμηση της Πρόγνωσης της νόσου
(Προγνωστικός Δείκτης
Prognostic Biomarker)

Ανάπτυξη



Διήθηση



Μετάσταση

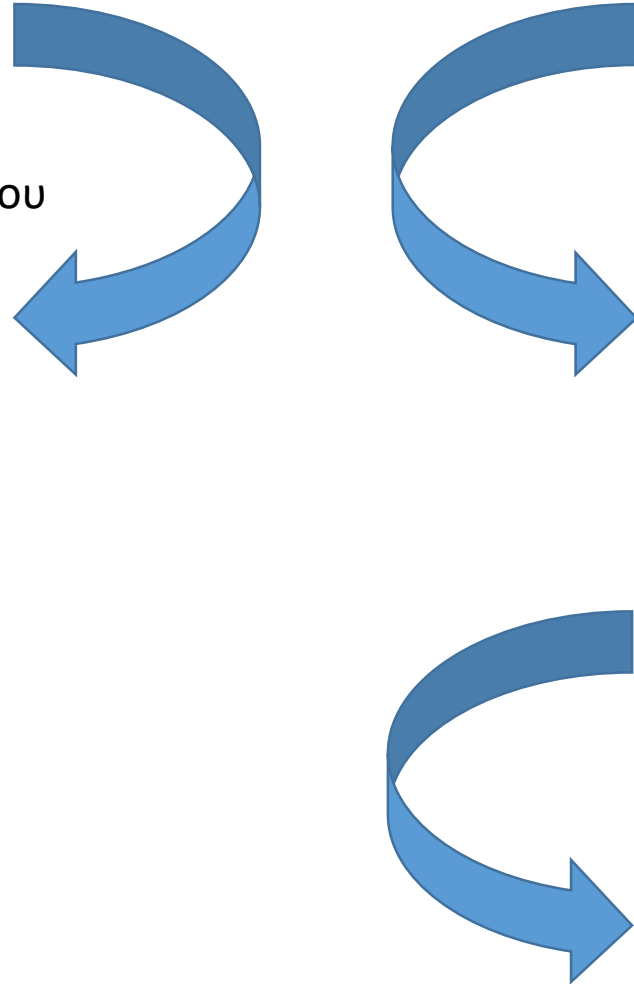


Εκτίμηση της Ανταπόκρισης στη Θεραπεία
(Προβλεπτικός Δείκτης
Predictive Biomarker)

Χημειοθεραπεία και Ακτινοθεραπεία

Εκτίμηση της ως στόχος για θεραπεία
(Therapy guiding Biomarker)

Αντι-Αγγειογενετική Θεραπεία
(αντιVEGF MoAbs – TK-inhibitors)



**ΕΚΤΙΜΗ ΤΗΣ ΑΓΓΕΙΟΓΕΝΕΣΗΣ
ΩΣ ΠΡΟΓΝΩΣΤΙΚΟΣ ΔΕΙΚΤΗΣ
ΣΕ ΑΣΘΕΝΕΙΣ ΜΕ ΝΕΟΠΛΑΣΙΕΣ**

ΚΛΑΣΣΙΚΟΙ ΠΡΟΓΝΩΣΤΙΚΟΣ ΔΕΙΚΤΕΣ ΣΕ ΑΣΘΕΝΕΙΣ ΜΕ ΝΕΟΠΛΑΣΙΕΣ

1. Μέγεθος του όγκου και τοπική διήθηση (T-stage)
2. Μετάσταση στους λεμφαδένες (N-stage)
3. Απομακρυσμένες μεταστάσεις (M-stage)

4. Ιστολογική διαφοροποίηση (Grade 1,2,3)

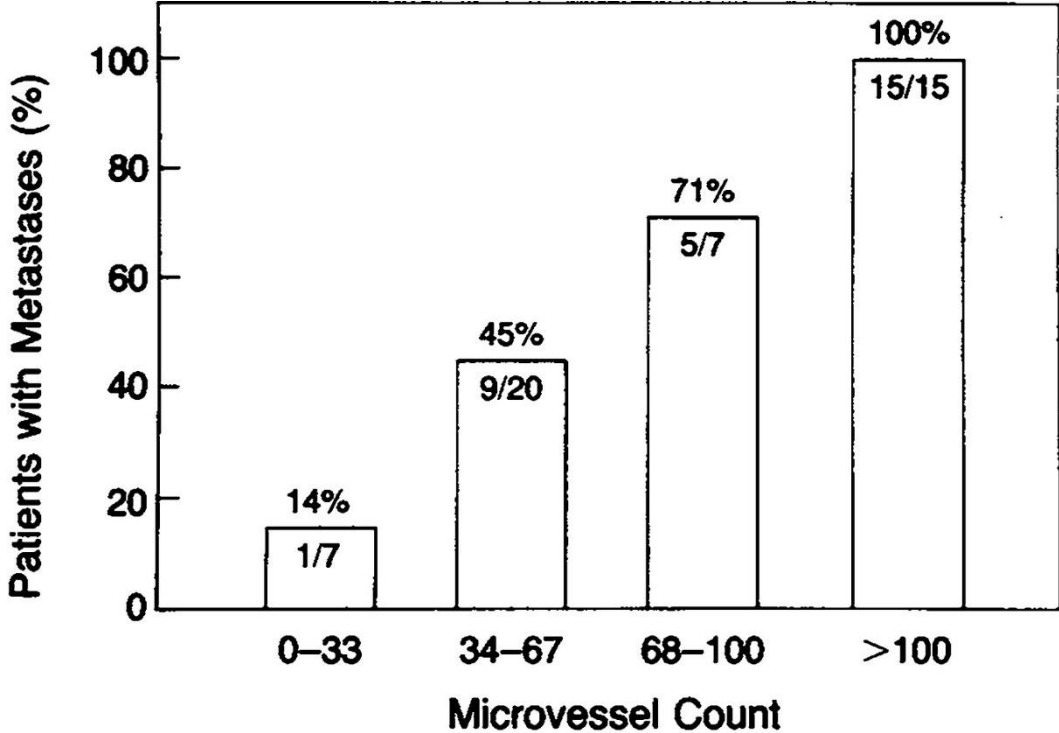
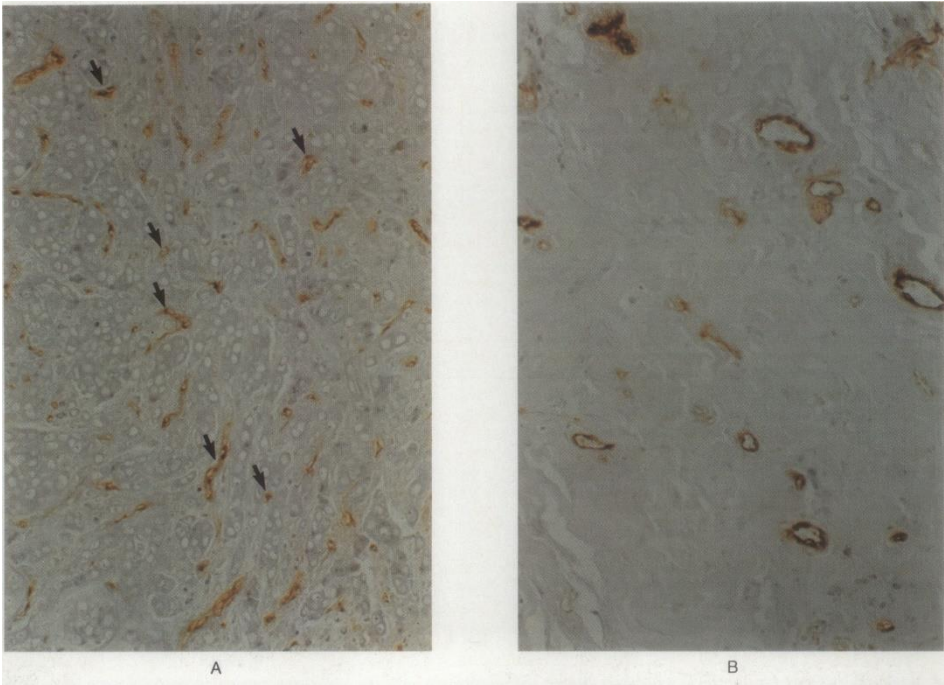
5. Ανοσοϊστοχημικοί δείκτες
 1. Her-2 (καρκίνος μαστού)
 2. Ki67 (δείκτης πολλαπλασιασμού)

6. Βιοχημικοί δείκτες
 1. PSA

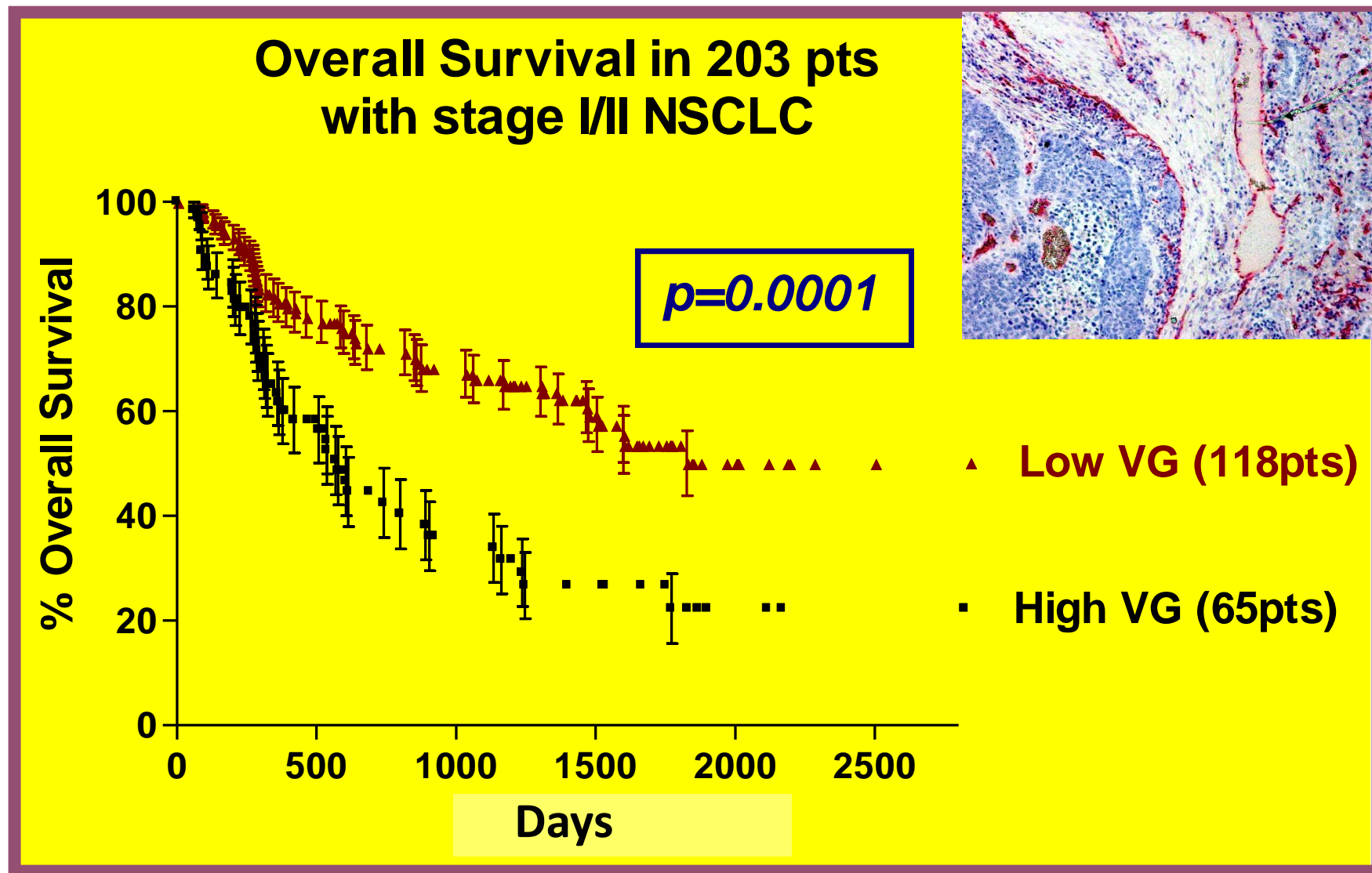


Dr. Judah Folkman, a professor at Harvard and director of the vascular biology program at Children's Hospital Boston, is considered the father of the idea that tumors can be kept in check by choking off the supply of blood they need to grow.

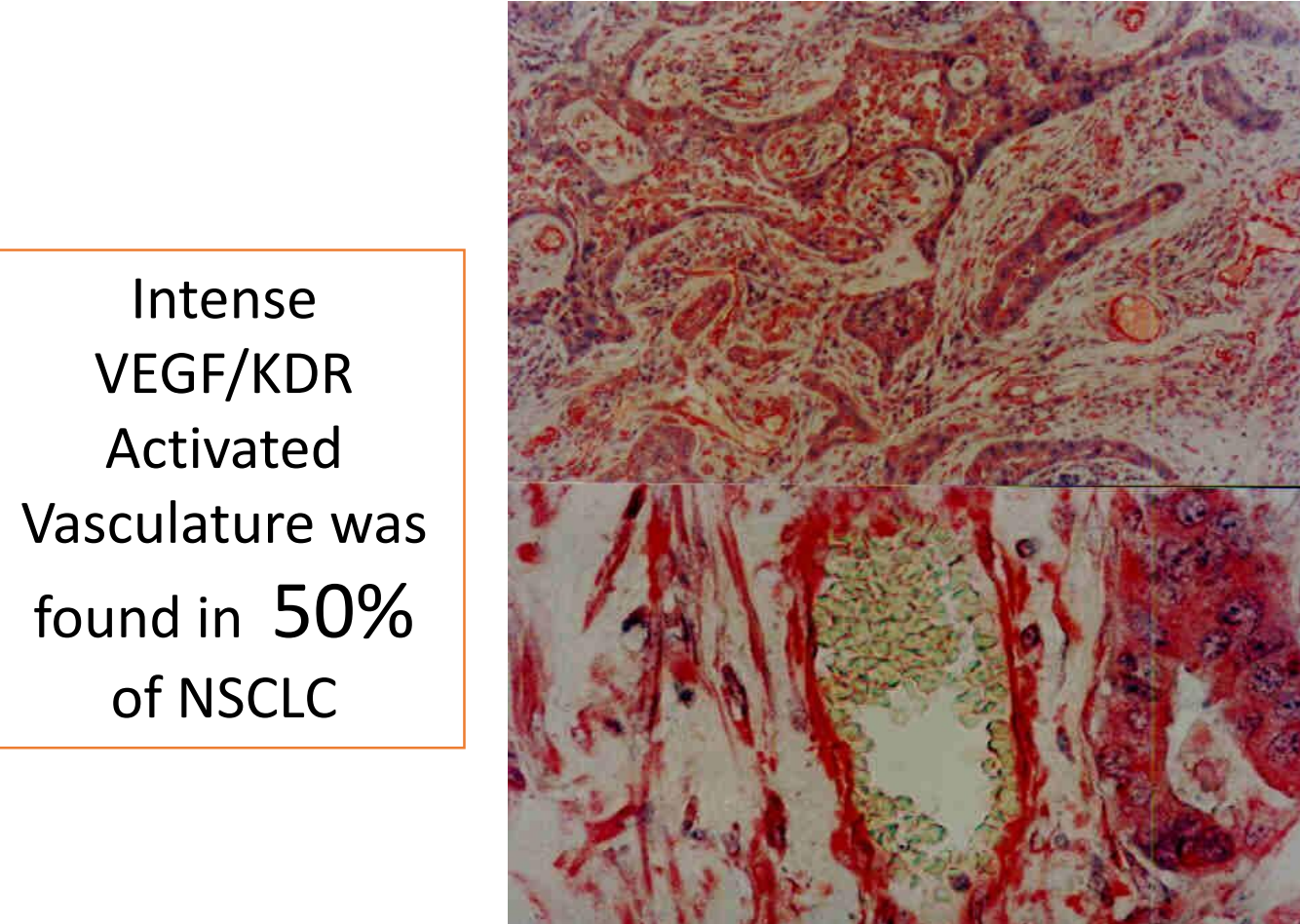
Weidner N, Semple JP, Welch WR, **Folkman J**. Tumor angiogenesis and metastasis--correlation in invasive breast carcinoma. N Engl J Med. 1991 Jan 3;324(1):1-8.



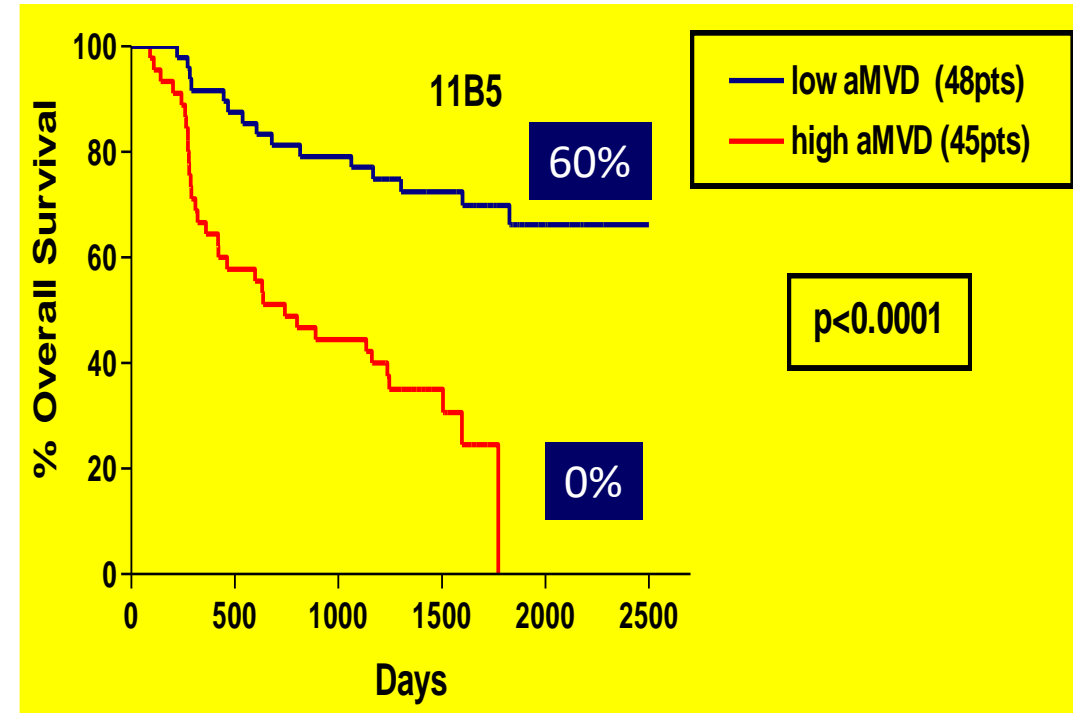
Giatromanolaki A, Koukourakis M, O'Byrne K, Fox S, Whitehouse R, Talbot DC, Harris AL, Gatter KC. Prognostic value of angiogenesis in operable non-small cell lung cancer. J Pathol. 1996 May;179(1):80-8.



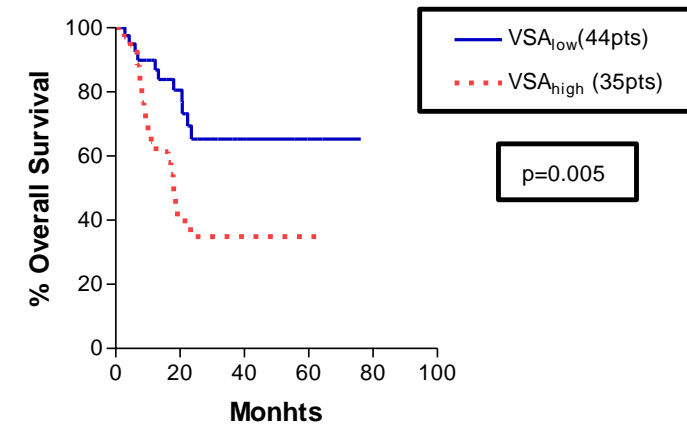
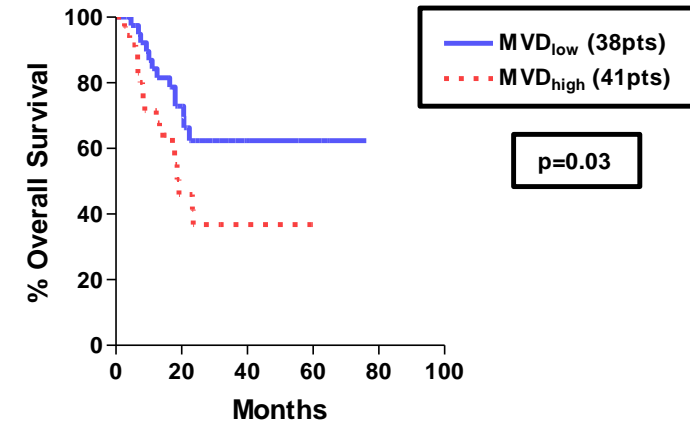
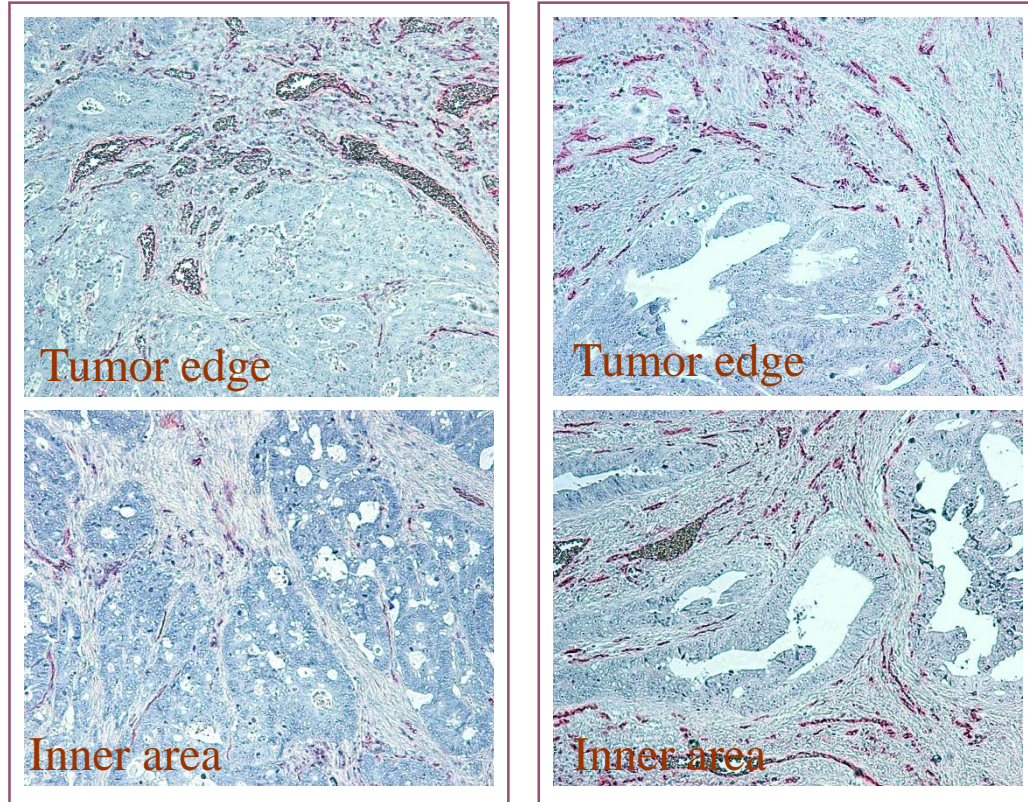
Koukourakis MI, Giatromanolaki A, Thorpe PE, Brekken RA, Sivridis E, Kakolyris S, Georgoulas V, Gatter KC, Harris AL. Activated Microvessel Density (aMVD) vs. CD31 standard MVD (sMVD) in non-small cell lung cancer . Cancer Res 2000 ; 60: 3088-3095



Intense
VEGF/KDR
Activated
Vasculature was
found in **50%**
of NSCLC



Giatromanolaki A, Sivridis E, Minopoulos G, Polychronidis A, Manolas C, Simopoulos C, Koukourakis MI. Differential assessment of vascular survival ability and tumor angiogenic activity in colorectal cancer. Clin Cancer Res 2002; 8:1185-1191

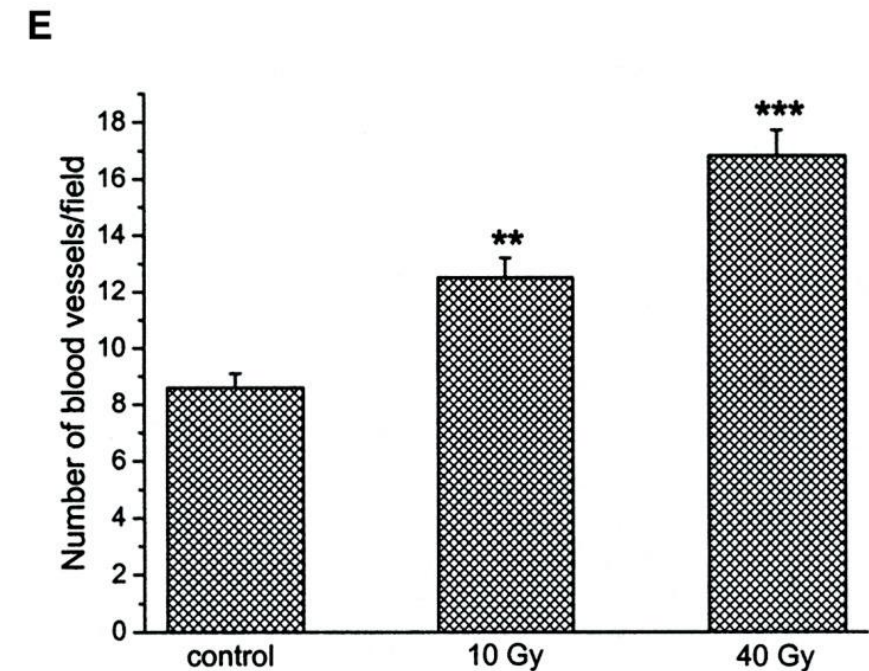
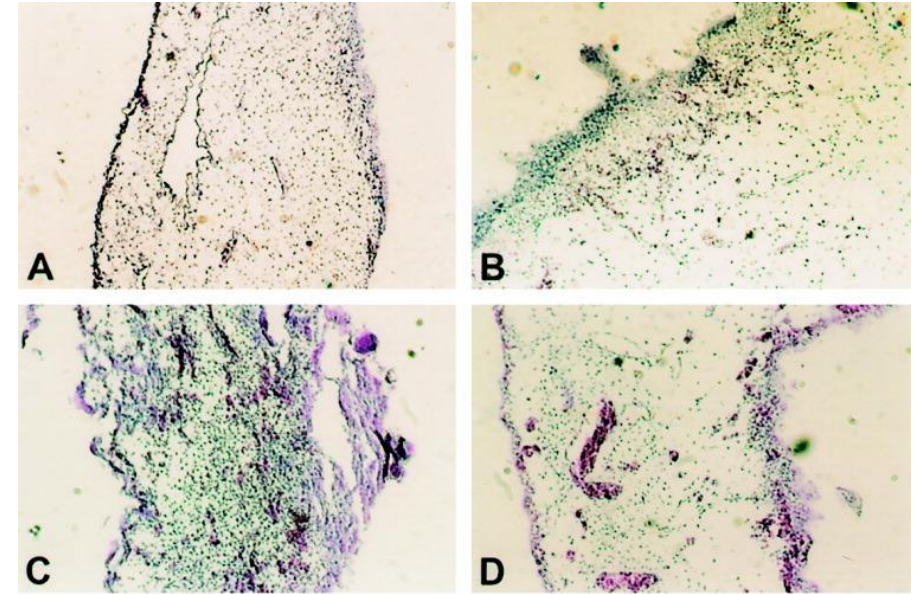


In multivariate analysis, VSA was the most important independent prognostic variable even within each of Dukes' stages separately.

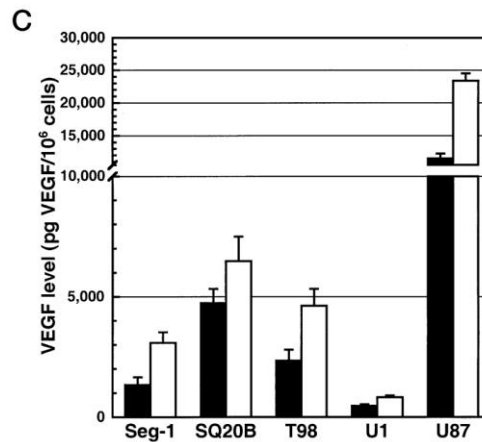
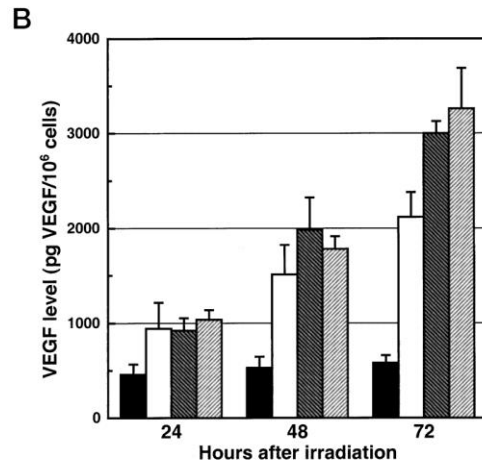
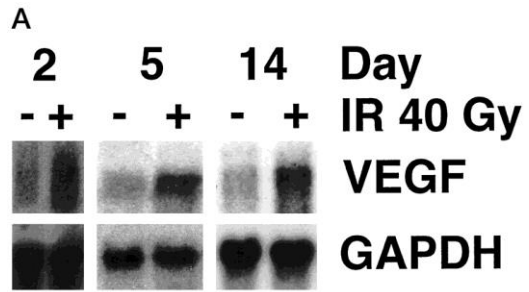
ΑΚΤΙΝΟΘΕΡΑΠΕΙΑ ΚΑΙ ΑΓΓΕΙΟΓΕΝΕΣΗ

Parthymou A, **Kardamakis D**, Pavlopoulos I, Papadimitriou E.
Irradiated C6 glioma cells induce angiogenesis in vivo and
activate endothelial cells in vitro. *Int J Cancer*. 2004 Jul
20;110(6):807-14.

These results explain at least in part the low effectiveness
of radiation therapy of malignant gliomas and support the
notion that inhibition of angiogenesis in parallel with
radiotherapy may represent a new therapeutic approach.

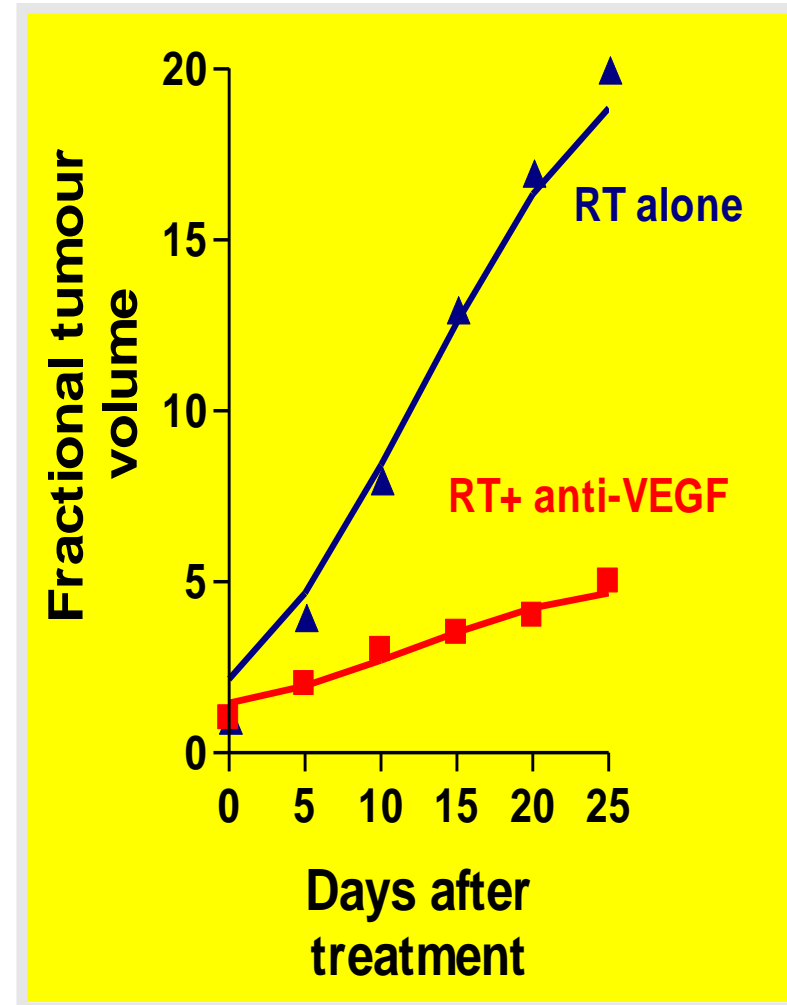


LLC and human tumor xenografts

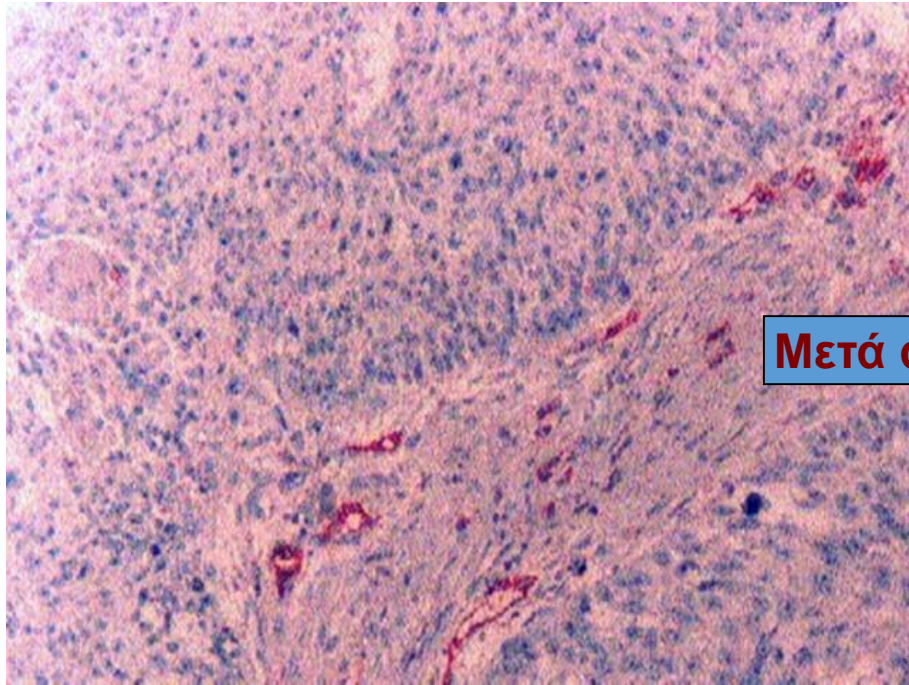


Gorski DH, Beckett MA, Jaskowiak NT, Calvin DP, Mauceri HJ, Salloum RM, Seetharam S, Koons A, Hari DM, Kufe DW, Weichselbaum RR. Blockage of the vascular endothelial growth factor stress response increases the antitumor effects of ionizing radiation. *Cancer Res.* 1999 Jul 15;59(14):3374-8.

University of Chicago

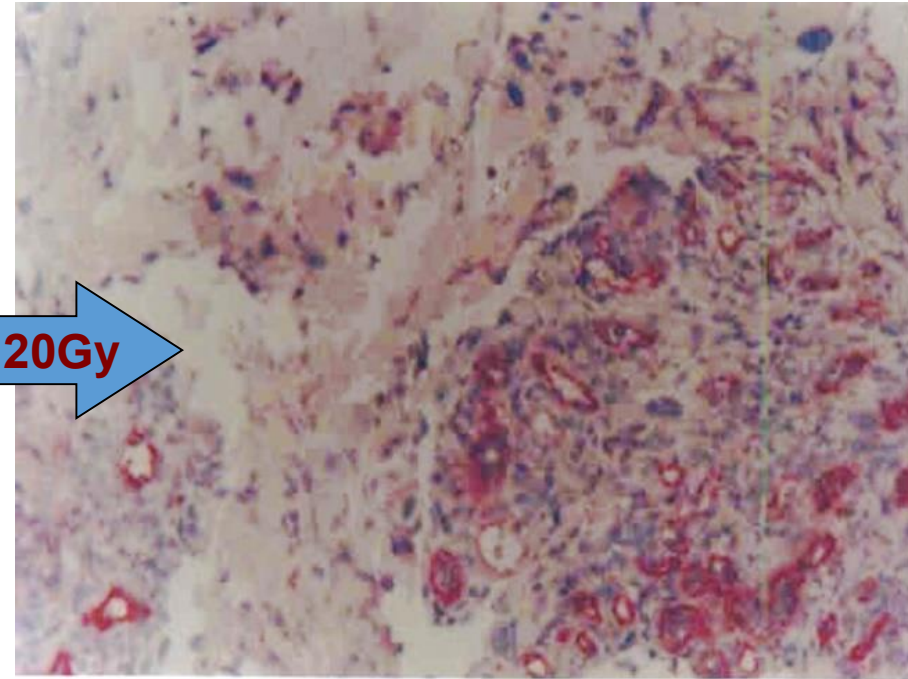


Koukourakis MI, Giatromanolaki A, Fountzilias G, Sivridis E, Gatter KC, Harris AL.
Angiogenesis, thymidine phosphorylase, and resistance of squamous cell head and
neck cancer to cytotoxic and radiation therapy. Clin Cancer Res. 2000 Feb;6(2):381-9.



Πριν την RT

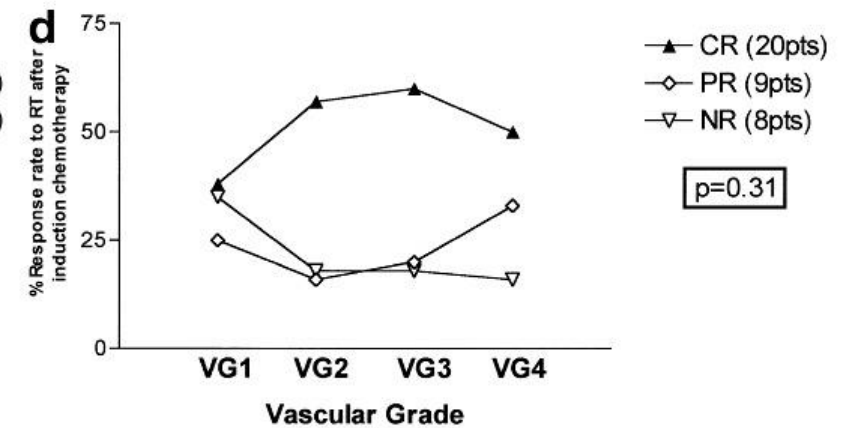
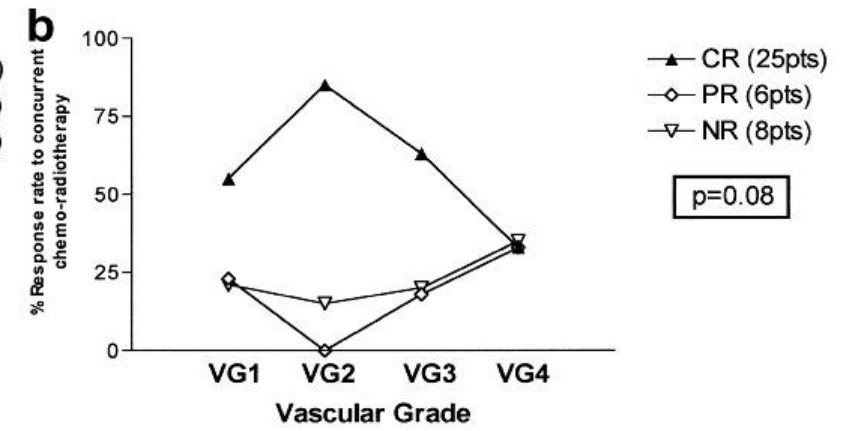
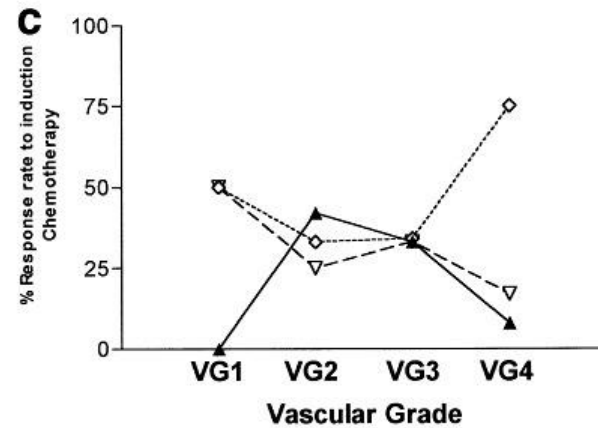
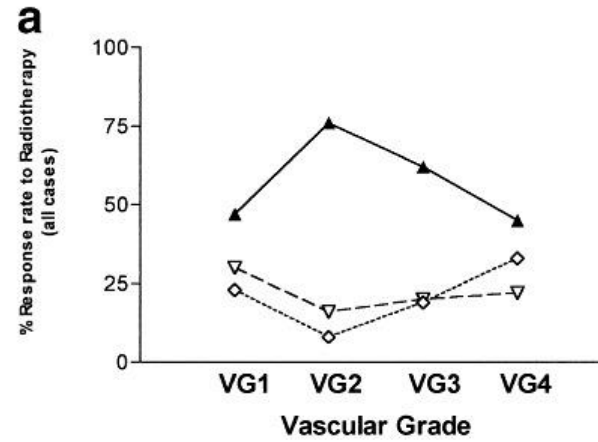
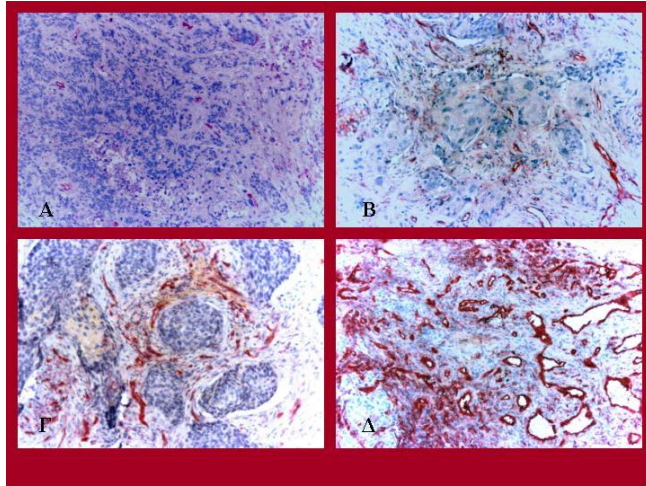
Μετά από 20Gy



Κατά τη διάρκεια της RT

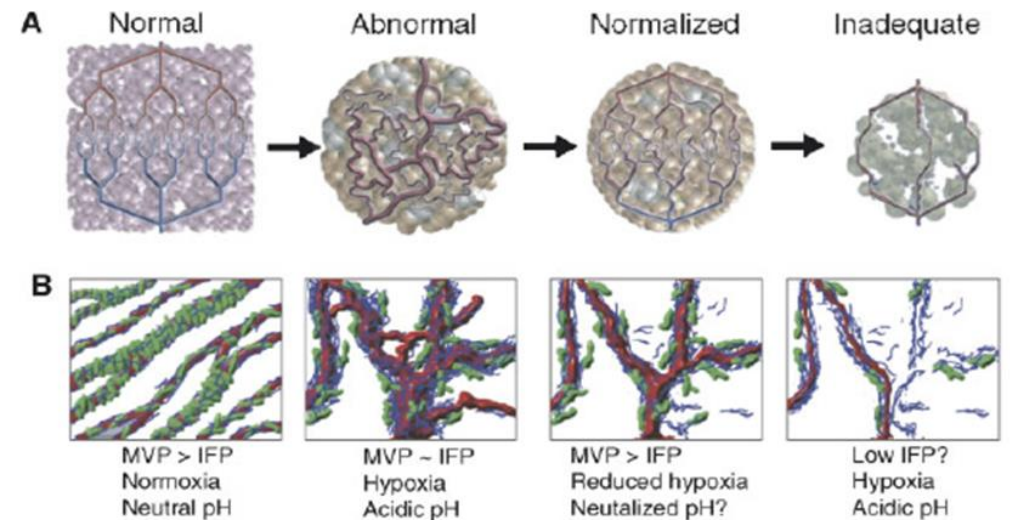
The concept of Angiogenic Regeneration

Giatromanolaki A, Koukourakis MI, Georgoulas V, Gatter KC, Harris AL, Fountzilias G. Angiogenesis vs. response after combined chemoradiotherapy of squamous cell head and neck cancer. *Int J Cancer*. 1999 Mar 15;80(6):810-7.

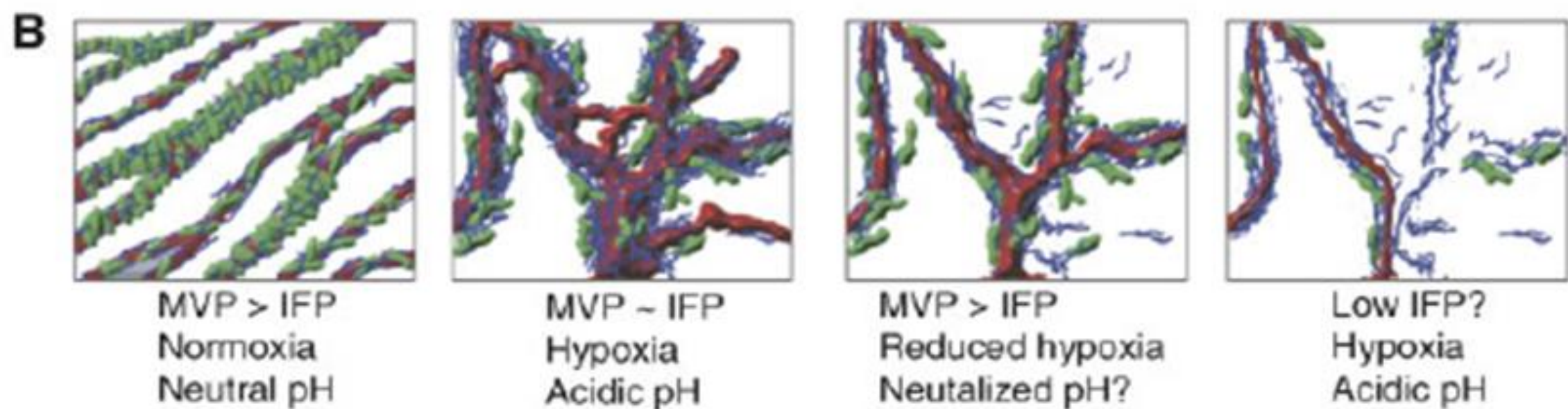
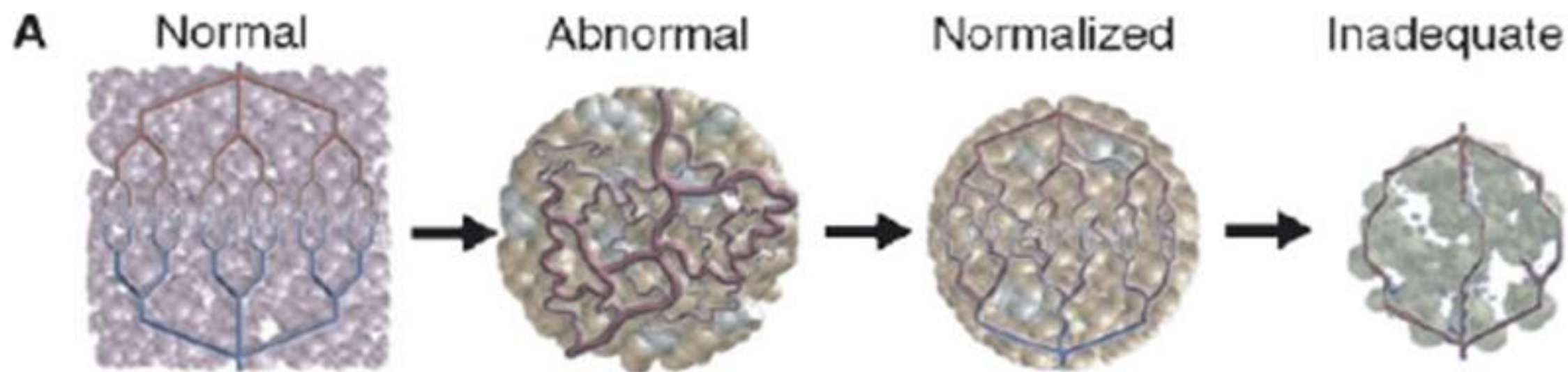


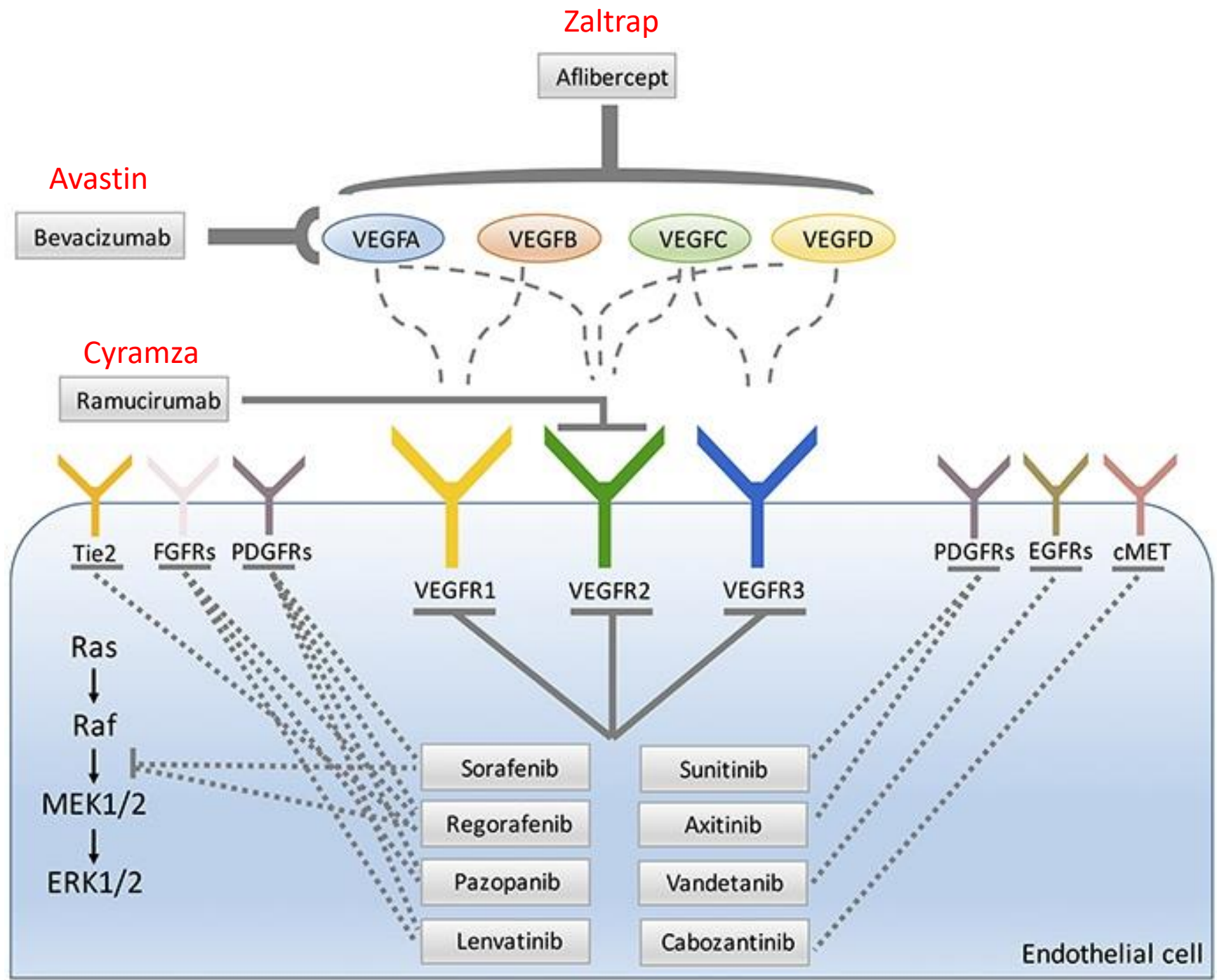
ΑΝΤΙ-ΑΓΓΕΙΟΓΕΝΕΤΙΚΗ ΘΕΡΑΠΕΙΑ

1. Καταστολή της ανάπτυξης των όγκων
2. Καταστολή της μεταστατικής δραστηριότητας
3. **VASCULAR NORMALIZATION**
 1. Αύξηση της διαθεσιμότητας της χημειοθεραπείας
 2. Αύξηση της αιματικής ροής – Φαινόμενο οξυγόνου



Willetts CG, et al. Direct evidence that the VEGF-specific antibody bevacizumab has antivascular effects in human rectal cancer. *Nat Med.* 2004 Feb;10(2):145-7.





Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, Berlin J, Baron A, Griffing S, Holmgren E, Ferrara N, Fyfe G, Rogers B, Ross R, Kabbinavar F. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med. 2004 Jun 3;350(23):2335-42.

813 ΑΣΘΕΝΕΙΣ ΤΥΧΑΙΟΠΟΙΗΘΗΚΑΝ ΝΑ ΛΑΒΟΥΝ

FL+irinotecan+bevacizumab (402) vs. FL+irinotecan+placebo (411).

Η ΑΝΤΑΠΟΚΡΙΣΗ

FL+irinotecan+bevacizumab 45%

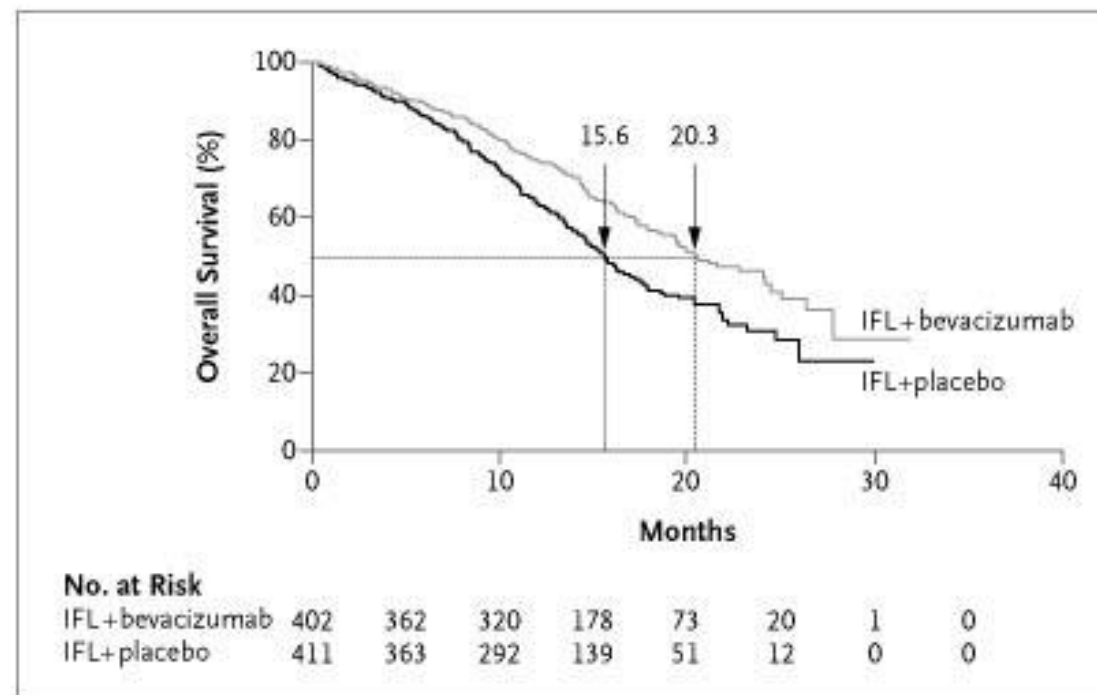
FL+irinotecan+placebo 35%

ΜΕΣΗ ΕΠΙΒΙΩΣΗ :

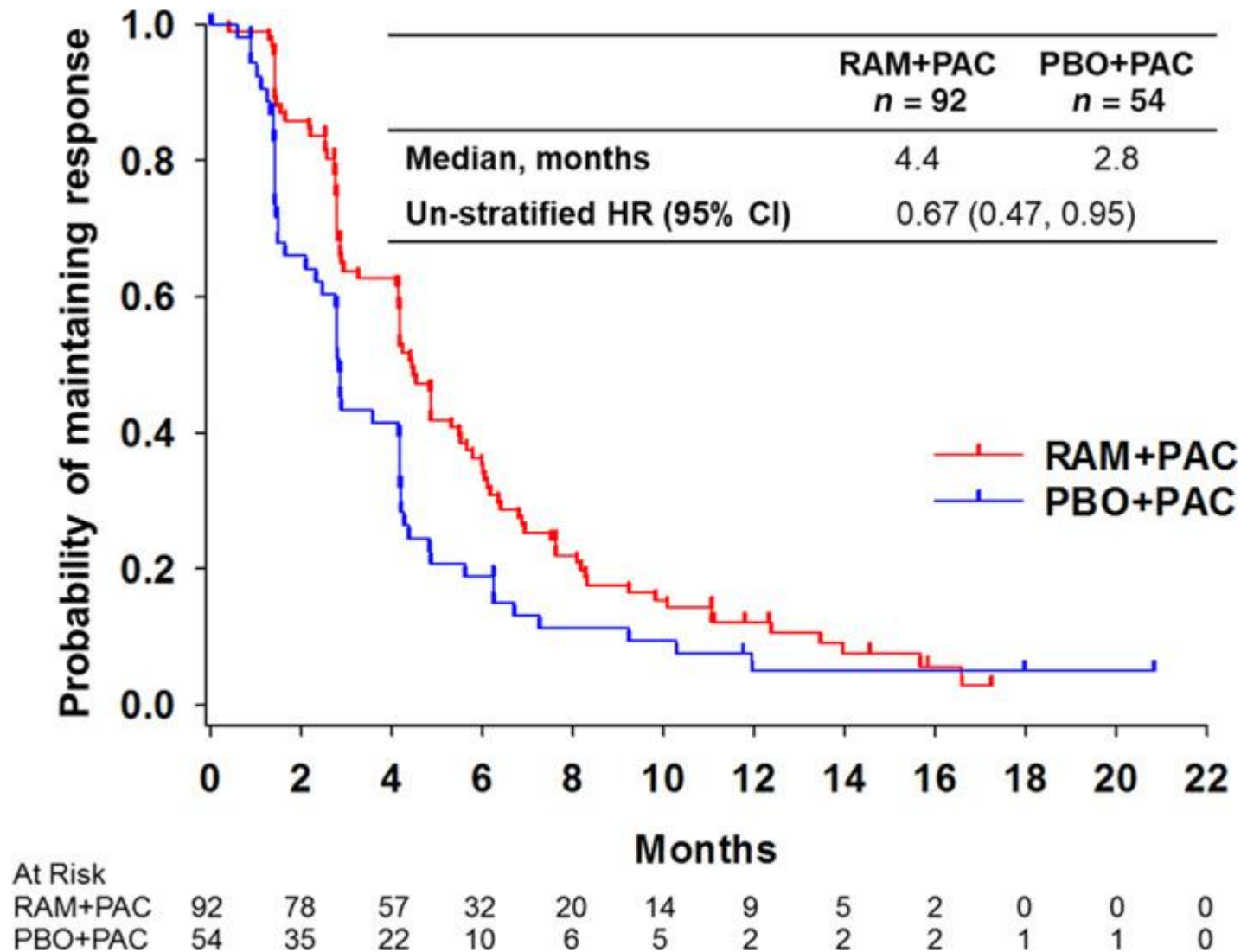
FL+irinotecan+bevacizumab 20.3 ΜΗΝΕΣ

FL+irinotecan+placebo 15.6 ΜΗΝΕΣ (P<0.001).

Colorectal Cancer

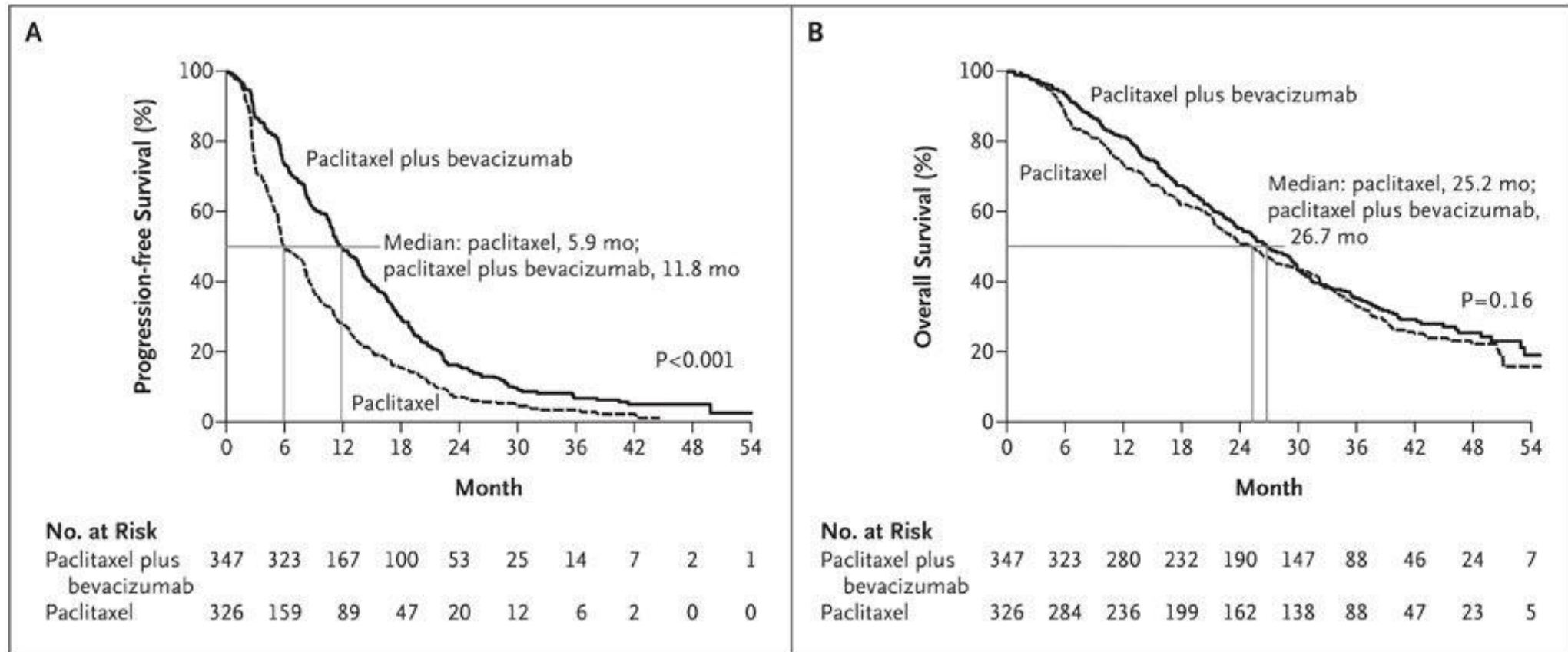


Gastric Cancer



Miller K, Wang M, Gralow J, Dickler M, Cobleigh M, Perez EA, Shenkier T, Cella D, Davidson NE. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. *N Engl J Med*. 2007 Dec 27;357(26):2666-76.

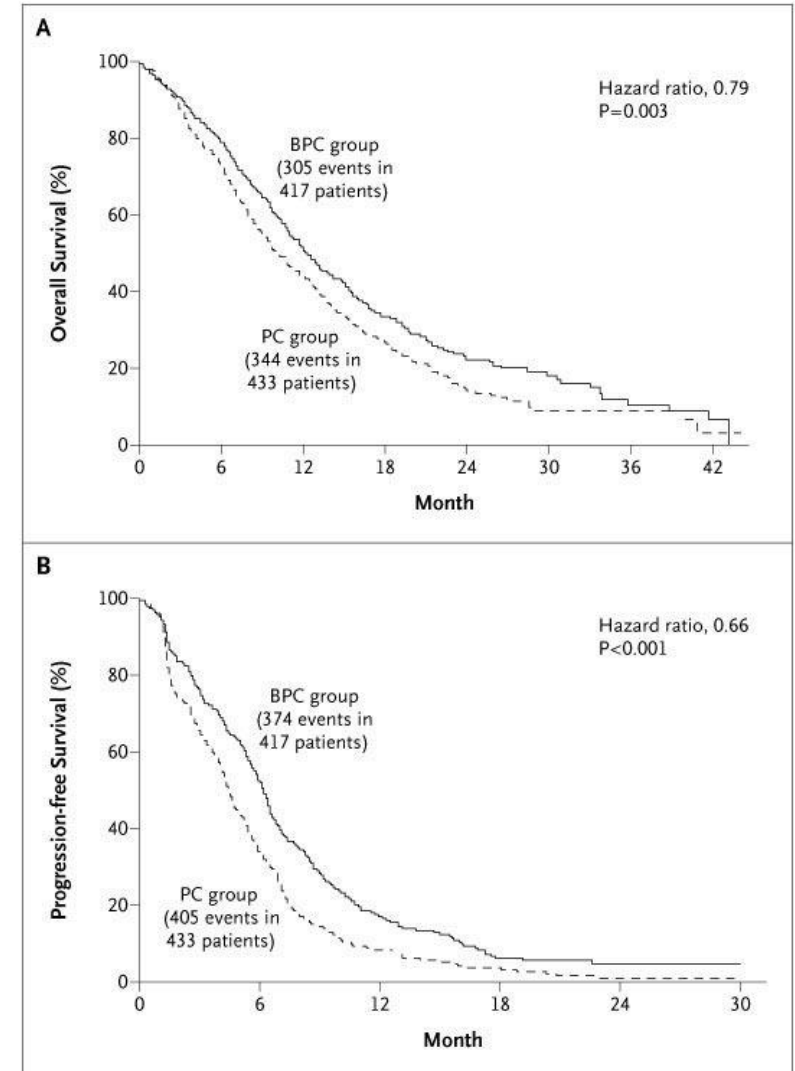
Breast Cancer



Sandler A, Gray R, Perry MC, Brahmer J, Schiller JH, Dowlati A, Lilienbaum R, Johnson DH. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med. 2006 Dec 14;355(24):2542-50.

Two deaths (from gastrointestinal hemorrhage and febrile neutropenia) occurred in patients in the paclitaxel-carboplatin group and 15 occurred in the paclitaxel-carboplatin-bevacizumab group;
Of the 15 deaths in the paclitaxel-carboplatin-bevacizumab group, 5 were attributed to pulmonary hemorrhage, 5 to complications of febrile neutropenia, 2 each to a cerebrovascular event or gastrointestinal hemorrhage, and 1 to a probable pulmonary embolus.

Non-Small Cell Lung Cancer



Koukourakis MI, Giatromanolaki A, Tsoutsou P, Lyrtzopoulos N, Pitiakoudis M, Kouklakis G, Chloropoulou PA, Manolas K, Sivridis E. Bevacizumab, capecitabine, amifostine, and preoperative hypofractionated accelerated radiotherapy (HypoArc) for rectal cancer: a Phase II study. *Int J Radiat Oncol Biol Phys.* 2011 Jun 1;80(2):492-8.

**Anti-VEGF therapy and Radiotherapy
Rectal Cancer**

