MEDICINA
USP 100 ANOS 1912 - 2012

INRAD
HCFMUSP

Desafios da medicina nuclear na atualidade

Marcelo Tatit Sapienza

2015 inac
INTERNATIONAL NUCLEAR ATLANTIC CONFERENCE

06/10/2015

DESAFIO

DESENVOLVIMENTO E INCORPORAÇAO DE CONHECIMENTO INTEGRADO

-modalidades híbridas - PET/CT, SPECT/CT, PET/RM

- Instrumentação
- Formacao medica e multiprofissional
- Busca da sinergia e complementaridade

-Imagem molecular

- Conceitos moleculares em medicina
- Biomarcadores
- Radiofarmacos

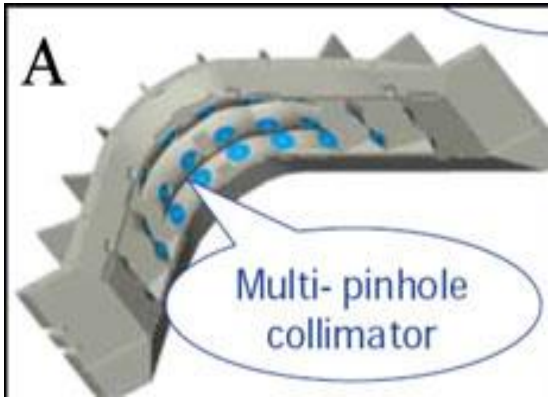
Instrumentação - Equipamentos

	Clinical PET	Clinical SPECT
Sensitivity	1%–3%	0.01%–0.03%
Resolution	~5 mm	~10 mm

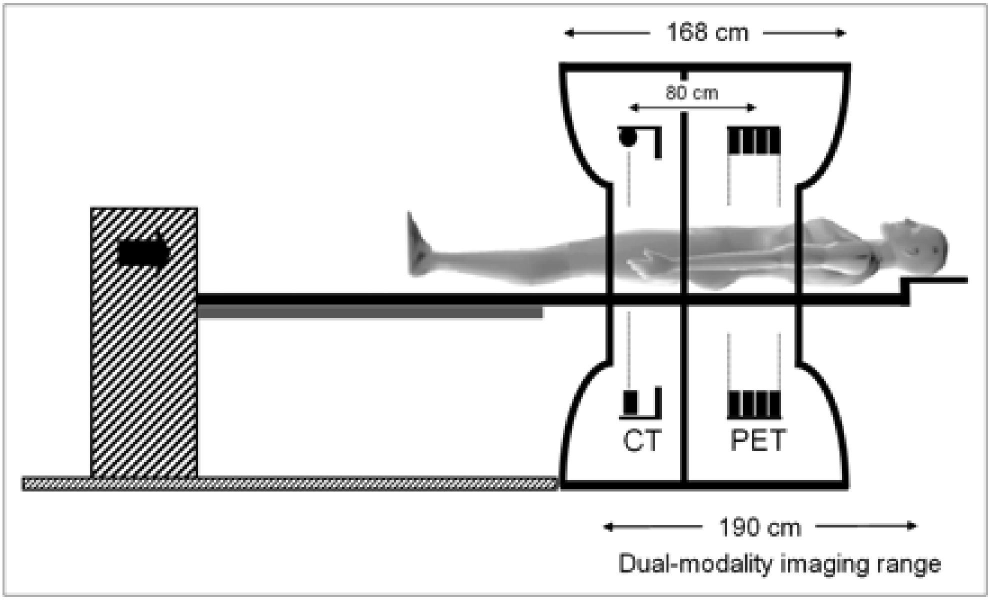
Jansen Nucl Med Biol 2007

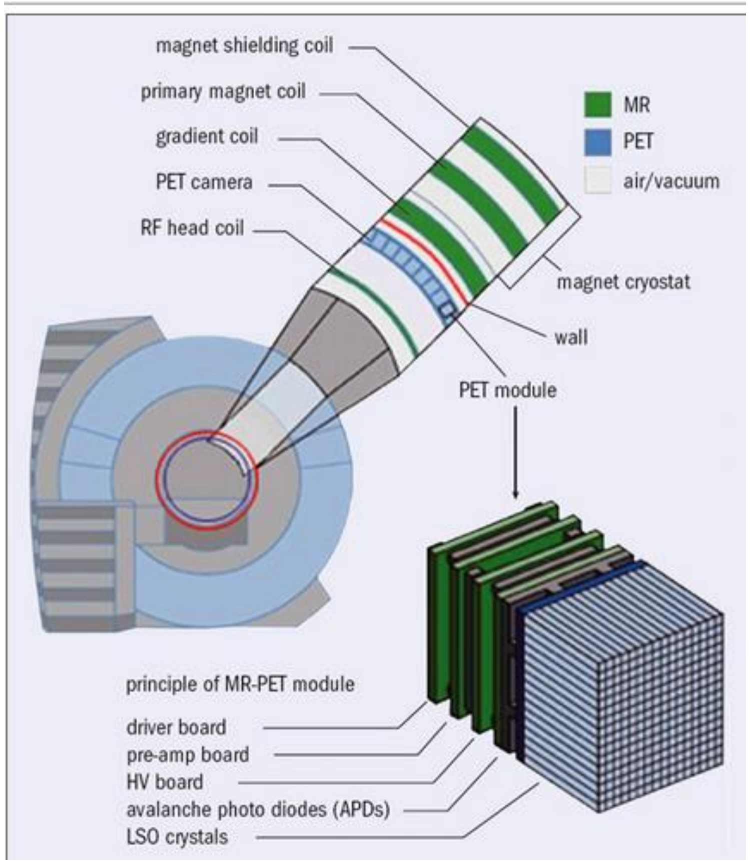
Equipamentos específicos

- Órgão alvo
- Sistema de detecção



PET/CT e PET/RM





Townsend JNM 2008

Lewis Cern 2008

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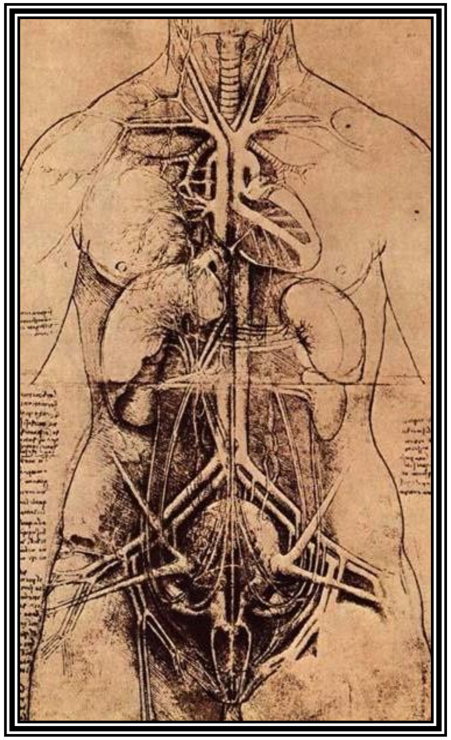
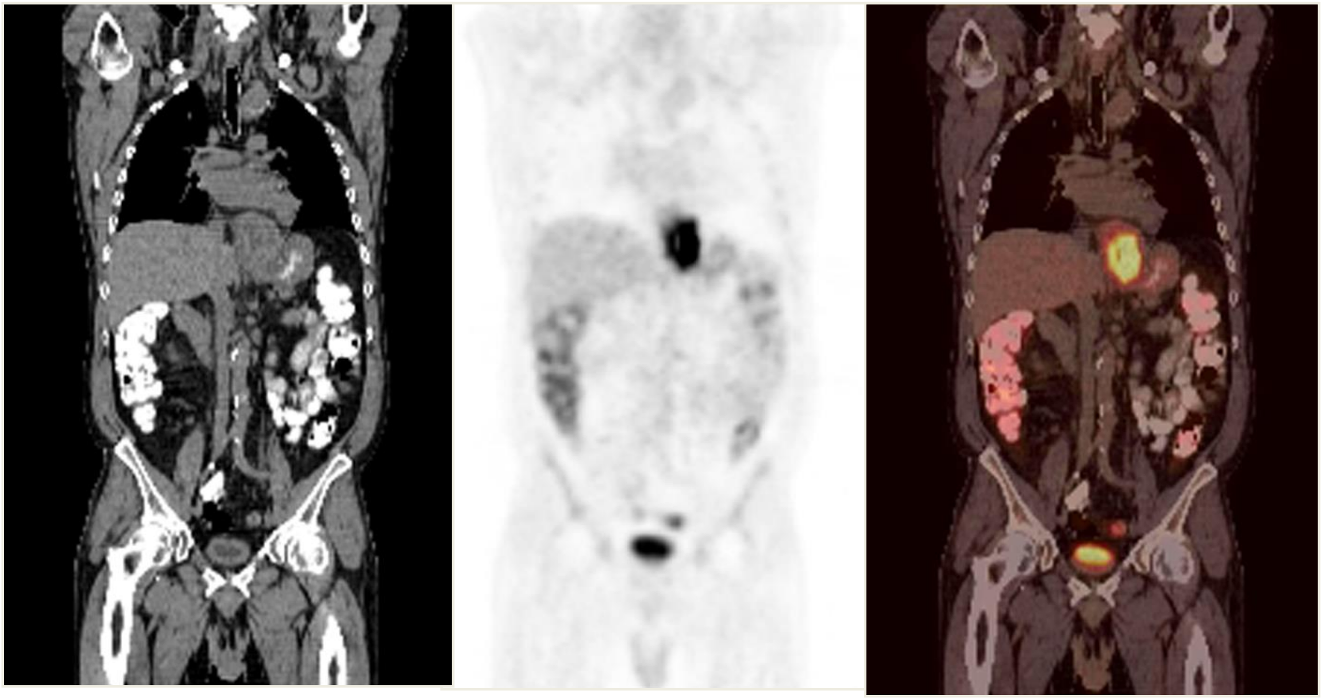
Correlação clínica
Integração e Análise Métodos Híbridos

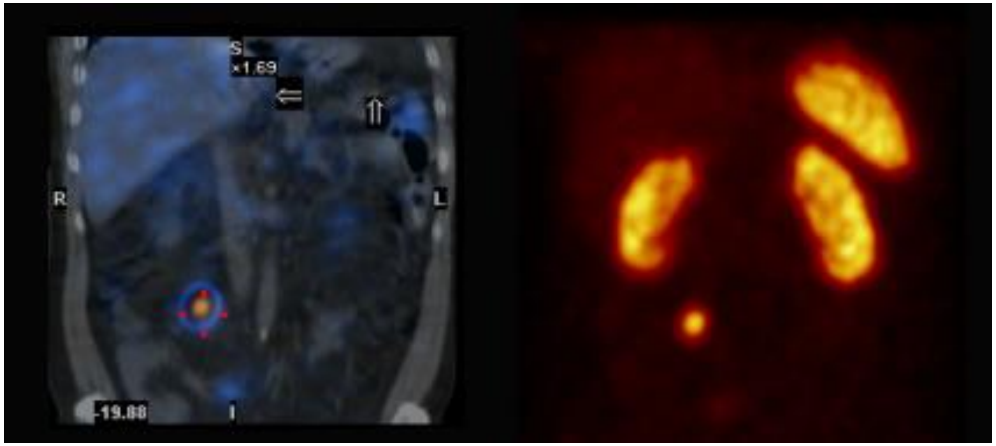




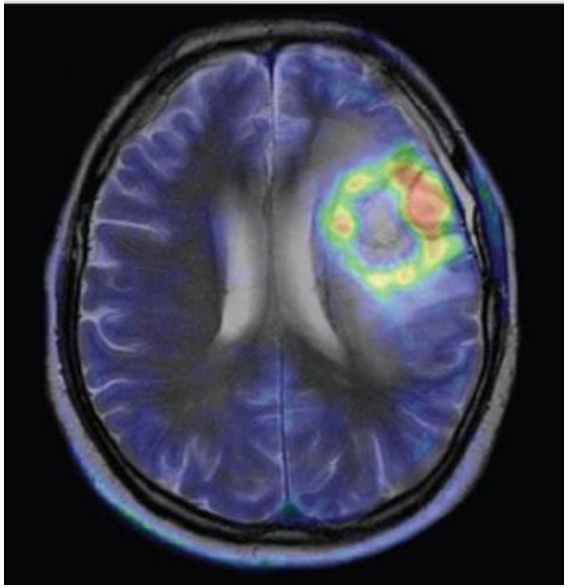
TC PET Fusão

recidiva CA esôfago

SPECT/CT



PET/RM



GE heatlhcare

INCORPORAÇÃO DE TECNOLOGIAS

Resultados	$
Sensibilidade Especificidade Impacto clínico	Custo e parque instalado equipamentos Duração do exame Insumos : Radiofármaco

Crise do Molibdênio / Tecnécio

NATURE NEWS 2007

nature Vol 450|13 December 2007

NEWS

Nuclear-reactor closure hits cancer tests

Hospitals across North America have been forced to cancel tests for cancer and heart disease because the unexpected closure of a Canadian nuclear reactor has led to a sudden shortage of medical isotopes.

The 50-year-old National Research Universal (NRU) reactor located in Chalk River, Ontario, was shut down on 18 November for scheduled maintenance and was due back online by mid-December. But Atomic Energy Canada, which owns and operates the facility, extended the outage to install safety-related equipment, including upgrades to the reactor cooling pumps. The reactor supplies about 60% of the molybdenum used in medical applications globally, including molybdenum-99, which decays into technetium-99m and is used in about 16 million nuclear medicine procedures annually in the United States.

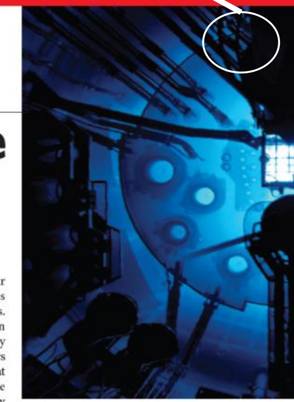
"It's a disaster for patients," says Sandy McEwan, president of the Society of Nuclear Medicine. North American hospitals now have 20–30% of the medical isotopes they require, he says.

Hospitals use a generator to extract technetium-99m from a source of decaying molybdenum-99. A technetium-99m isotope has a useful life of about one week, but can be stretched to two. MDS Nordion, an Ottawa-based life-sciences firm and molybdenum supplier to Bristol-Myers Squibb Medical Imaging, says it expects shortages of the radioisotope until mid-January. Molybdenum-99 has a half-life of 66 hours and cannot be stockpiled. Reactors in Australia, South Africa and Brussels also produce molybdenum-99. The shortage has

NATURE|Vol 460|… July 2009

Medical isotope shortage reaches crisis level

Robust solutions sought urgently to shore up fragile supply chain.



T. TAPSELL, ANSTO

The worldwide shortage of medical isotopes is about to get much worse this week, as the High Flux Reactor in Petten, the Netherlands, closes for a month-long maintenance inspection.

It joins the National Research Universal reactor in Chalk River, Ontario, Canada, which has been closed since 15 May because of a heavy-water leak and is unlikely to restart before late 2009, according to Atomic Energy of Canada Limited, the government-sponsored body that runs the facility.

Together, the reactors produce two-thirds of the global supply of molybdenum-99, which decays to form technetium-99m, an isotope that is used in about 70,000 medical imaging procedures worldwide every day.

The shutdown has prompted calls for a major review of the way that medical isotopes are made and distributed. All five commercial nuclear reactors that use neutron-induced fission of highly enriched uranium-235 to make ^{99}Mo (see map) are more than 40 years old and cracks are beginning to emerge. The Petten reactor is scheduled to close again in early 2010 for up to six months so that deformed pipes in its cooling system can be repaired.

With both reactors unavailable for significant periods, "you really do have to say: 'right, let's clear the table and start all over'", says Thomas Ruth, senior research scientist at TRIUMF, Canada's national laboratory for particle and nuclear physics in Vancouver.

The problem arises because isotopes cannot be stockpiled — ^{99}Mo has a half life of 66 hours and ^{99m}Tc of just six hours. ^{99}Mo created in nuclear reactors must be shipped quickly to facilities that process the material into ^{99m}Tc generators. These generators are delivered to hospitals on a weekly basis, where they are 'milked' every morning to deliver ^{99m}Tc. Although the reactors in Belgium and South Africa will be working at full power over the next few weeks to produce more ^{99}Mo than usual, isotope suppliers say they will probably not be able to meet the shortfall. The shortage has been particularly acute in the United States and Canada, and "the situation will get much worse", says Michael Graham, director of nuclear medicine at the University of Iowa in Iowa City, and president of the international Society of Nuclear Medicine based in Reston, Virginia. "It is likely many studies will be cancelled or postponed."

Leaky pipeline

Week-by-week availability of ^{99}Mo is now coordinated by the Brussels-based Association of Imaging Producers and Equipment Suppliers (AIPES), which in the past year has taken the initiative to stimulate global action on the isotope crisis. Both the AIPES and the Organisation for Economic Co-operation and Development (OECD), based in Paris, began to investigate long-term solutions to the chronic shortage of ^{99}Mo at the start of 2009. But given the importance of ^{99m}Tc in health care, the ageing reactor infrastructure and highly fragmented supply network needs a root-and-branch overhaul.

"We must upgrade and invest in updates to these ageing reactors," says George Segall, chief of the nuclear-medicine service at the Veterans' Affairs Palo Alto Health Care System in California. "Many of these reactors have already exceeded their useful lifetime. No one expected that they would still be needed now when they were built."

The Canadian government has so far resisted calls to switch on two Multipurpose Applied Physics Lattice Experiment (MAPLE) reactors, built at the Chalk River site to replace the 52-year-old National Research Universal reactor. The MAPLE reactors were to be the first nuclear reactors in the world dedicated to production of medical isotopes, but are lying dormant after Atomic Energy of Canada Limited halted development in May 2008, citing safety issues that it claimed it would be too expensive to resolve. If started up, these reactors alone could deliver more than the current global requirement for medical isotopes, according to Harold Smith, who was a manager on the MAPLE project.

Some medical-isotope suppliers are looking to academic research reactors to fill the gap. MDS Nordion, a medical-isotope provider based in Ottawa, Canada, that had invested heavily in the ill-fated MAPLE project, is negotiating with the Karpov Institute of Physical Chemistry in Moscow, which holds a 90% share of the market for ^{99m}Tc generators in Russia.

Researchers at Germany's Technical University of Munich are seeking financial backing from the government to support an upgrade to the university's FRM II neutron source to create ^{99}Mo. If highly enriched ^{235}U targets were used, the reactor could satisfy almost all of Europe's needs for ^{99m}Tc once it becomes fully operational, says Winfried Petry, scientific director of the FRM II.

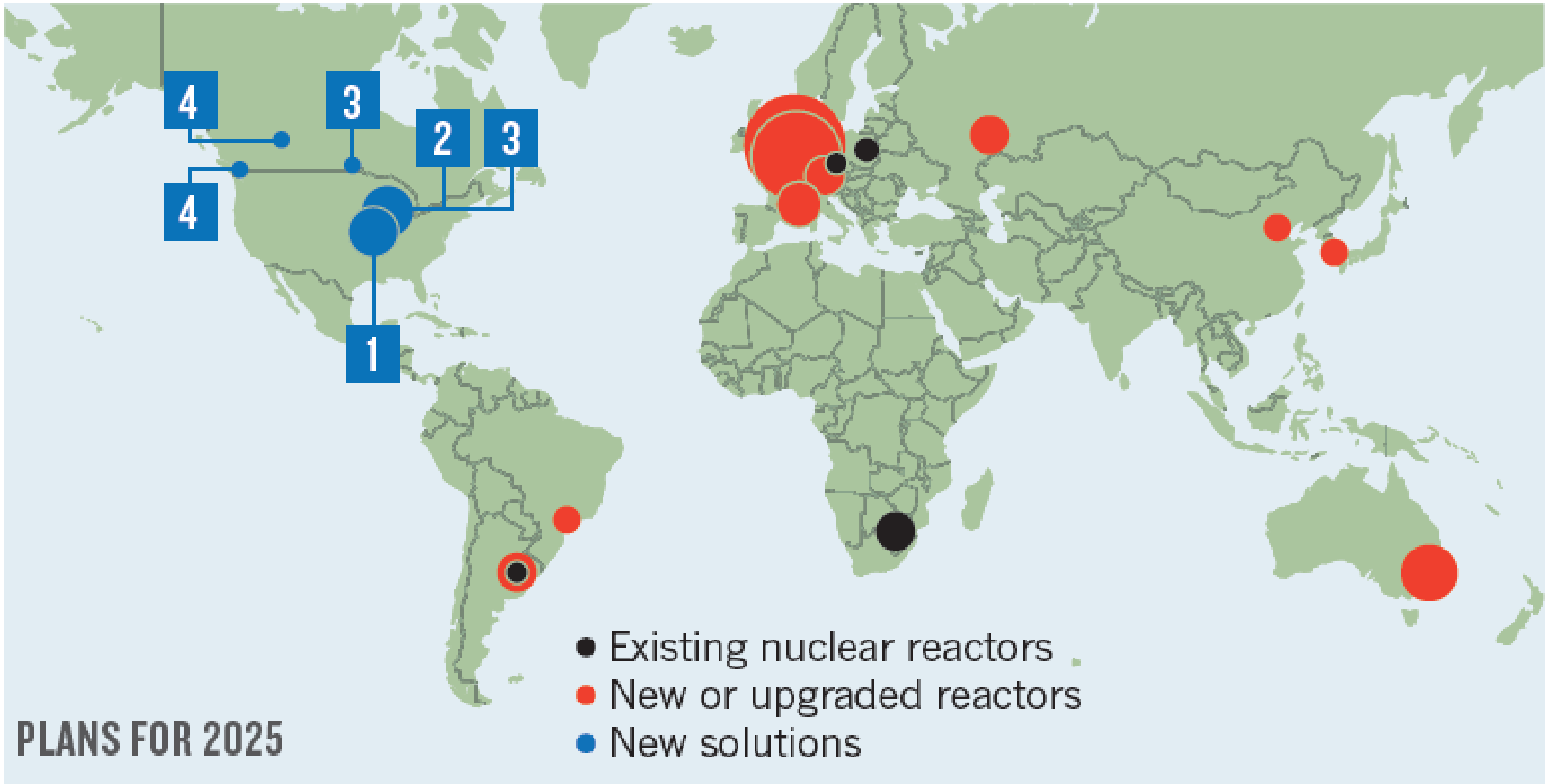
An alternative option, says Ruth, could be to fire high-energy electrons at ^{100}Mo targets, forcing out a neutron to create ^{99}Mo. This

SOURCE: LANTHEUS MEDICAL IMAGING

THE MEDICAL TESTING CRISIS

With a serious shortage of medical isotopes looming, innovative companies are exploring ways to make them without nuclear reactors.

BY RICHARD VAN NOORDEN



Reator Multipropósito Brasileiro (RMB)

Ministério de Ciência, Tecnologia e Inovação

- Gerador ^{99}Mo-^{99m}Tc: tecnécio-99m > 80% MN diagn
- Outros radionuclídeos (iodo-131, lutécio-177)

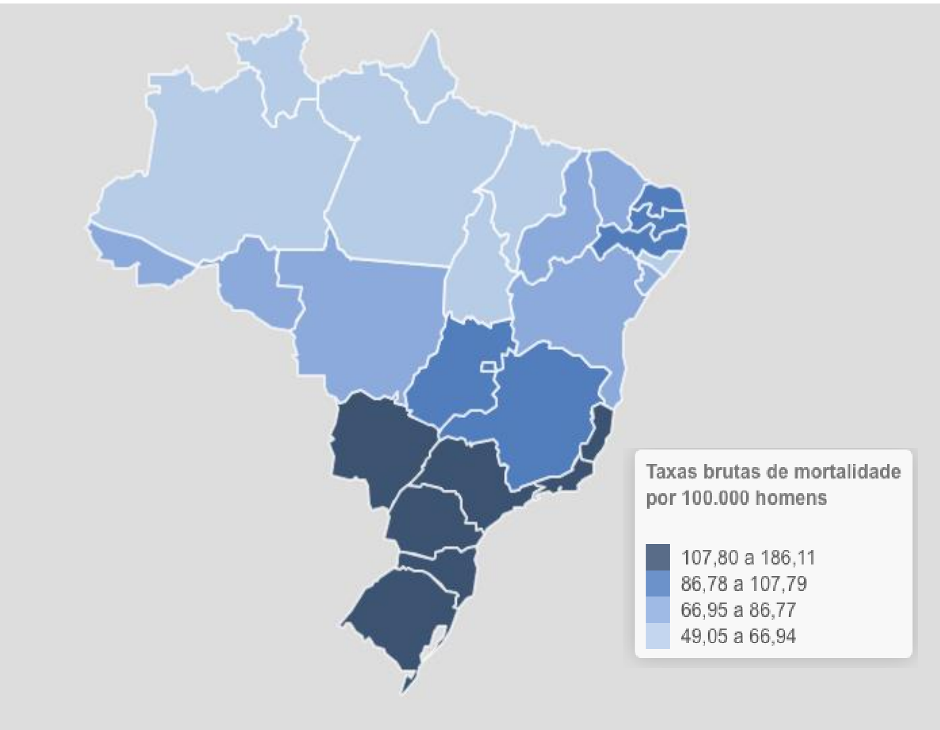
Compreensão Molecular da doença

Células anormais com alterações fenotípicas / moleculares

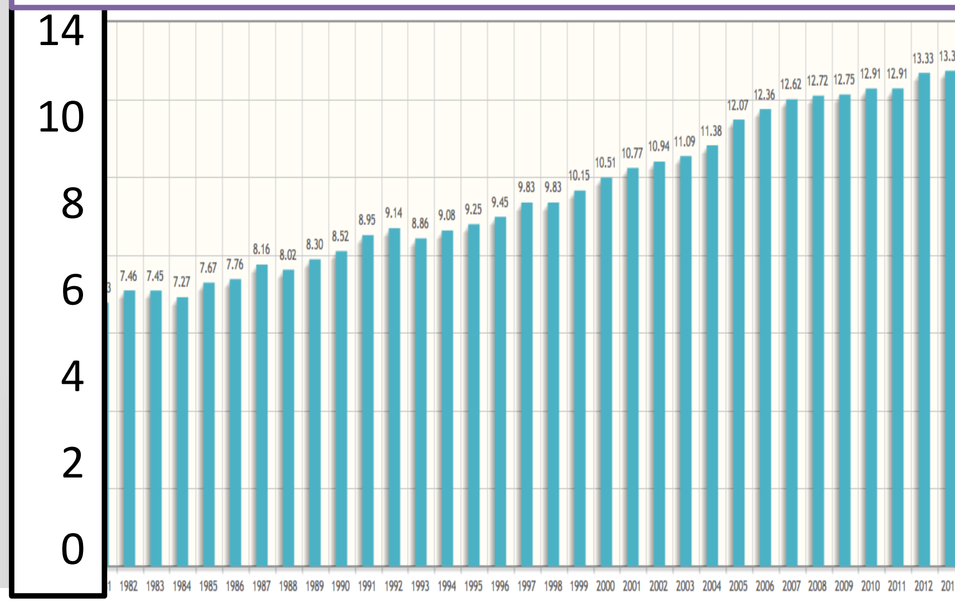
Desenvolvimento de ligantes para imagem

- DIAGNOSTICO
- RESPOSTA A TERAPIA
- ALVO MOLECULAR
- TERAPIA
- NOVAS DROGAS
- PLANEJAMENTO DE TERAPIA (RT, MN)

Câncer

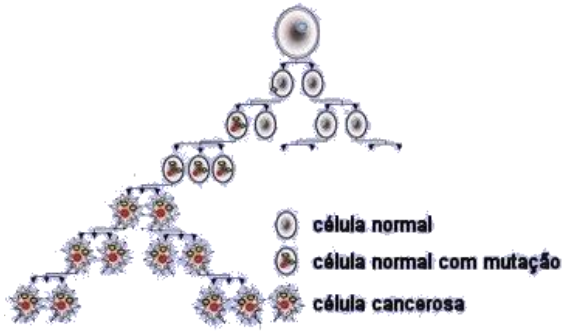


•*Mortalidade por 100.00 habitantes entre 1980 e 2013 (INCA)*



Neoplasias malignas

- Crescimento desordenado
- Invasão
- metastases



Classificadas

<u>pelo local de origem</u> →

Pele (ñ melanoma)
Mama
Pulmão
Estômago
Colo útero
Próstata
Cólon e reto
Esôfago
Leucemia
Boca
Melanoma

<u>pelo tipo celular</u>:

epitelial (pele / mucosa): **carcinomas**

conjuntivo (osso, músculo, cartilagem): **sarcomas**

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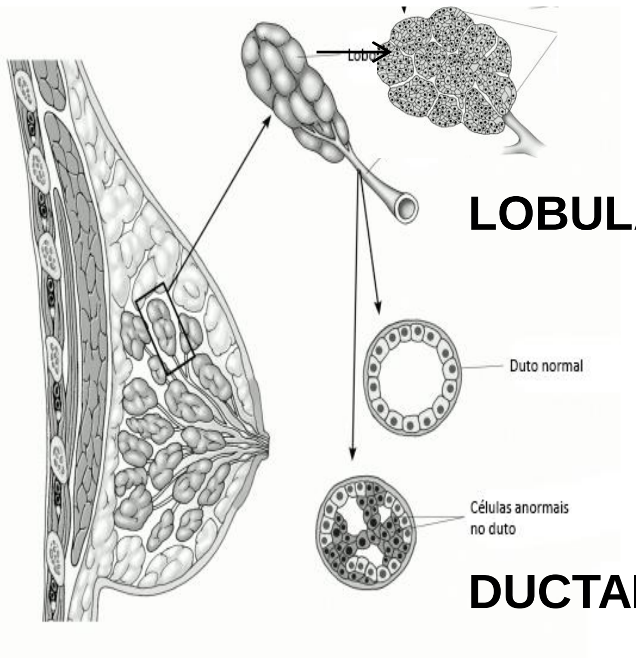
Câncer: classificacao

Origem – ex.: CA mama



LOBULAR

DUCTAL

Outros...

Estadiamento

AJCC Cancer Staging Manual. 7ed. 2010

T 1 < 2 cm **T2** 2-5 cm
T3 > 5 cm **T4** parede / pele

N1 axilar I /II móvel,
N2 axilar fixo ou mamaria,
N3 infraclav(III) / axila+mamaria / supraclav

Metástases

PROGNOSTICO e CONDUTA

*Estadiamento **TNM***

Modificações tratamento

localizado x sistêmico

Prognóstico

• mama	Sobrevida 5 anos	localizado = **90 %**	metas **15 %**
• próstata	Sobrevida 5 anos	localizada ~**100 %**	metas **35 %**
• pulmão	Sobrevida 5 anos	localizada **50-70 %**	metas **< 5 %**

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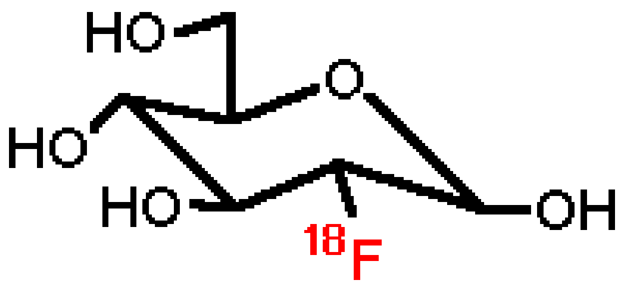
PET CT com FDG no câncer

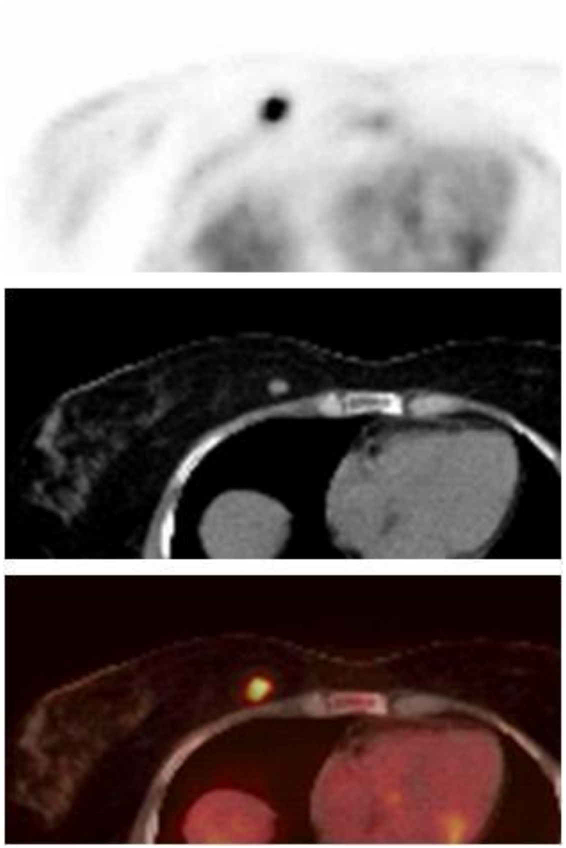
Metabolismo de glicose

- Transporte (Glut)
- Fosforilação (hexoquinase)
- Aumento do metabolismo

Imagem molecular ou contraste ?



PET FDG em CA de mama



<u>Detecção do tumor</u>

- **S**: 80-100% **E**: 75-100%

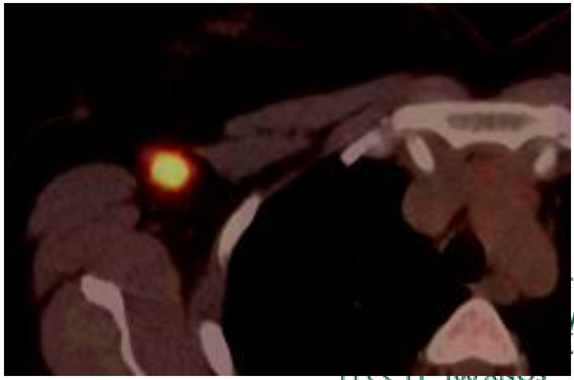
<u>Estadiamento Nodal Axilar</u>

- **S**: 37% **E**: 96 %

<u>Estadiamento a distância</u>:

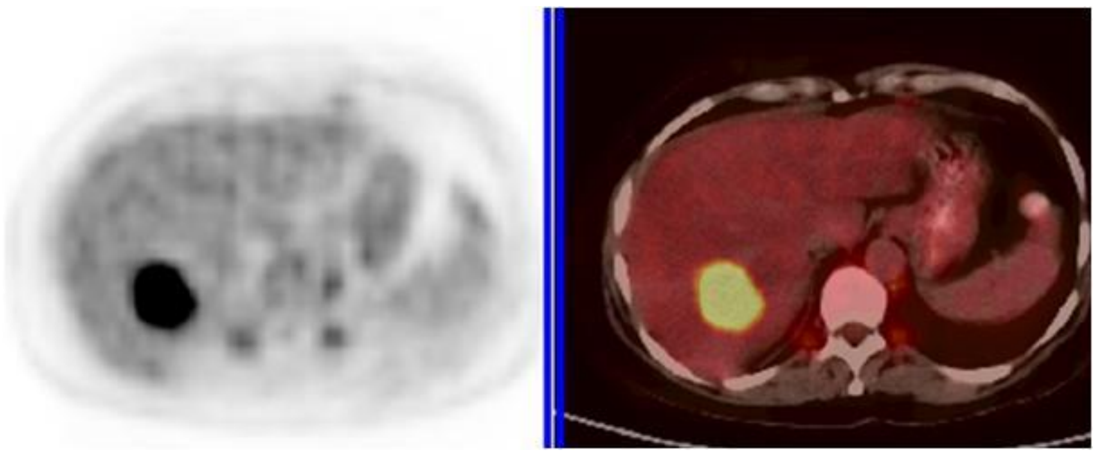
- inicial para doença avançada
- <u>considerar</u> para III ou IV duvidoso
- **muda o estadio em 28% casos (meta e N3).**

Groheux D JNM 2011



PET FDG em CA de mama

Suspeita de Recorrência

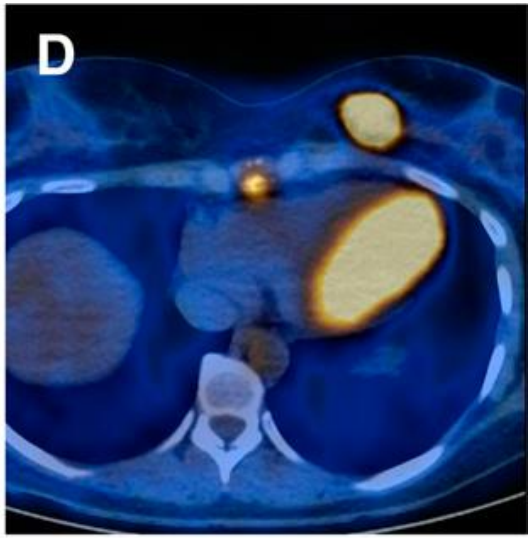


S 93%   E 82% muda conduta 30%

… algo a mais na imagem

Valor Prognóstico: ↑ SUVmax ↓ sobrevida

Fletcher JW,. J Nucl Med. 2008



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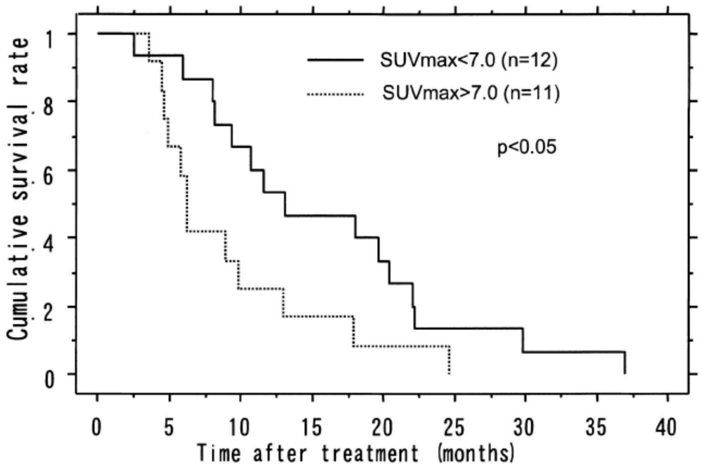
Prognóstico - SUV em diferentes tumores



Pâncreas - J Hepatobiliary Pancreat Surg, 200

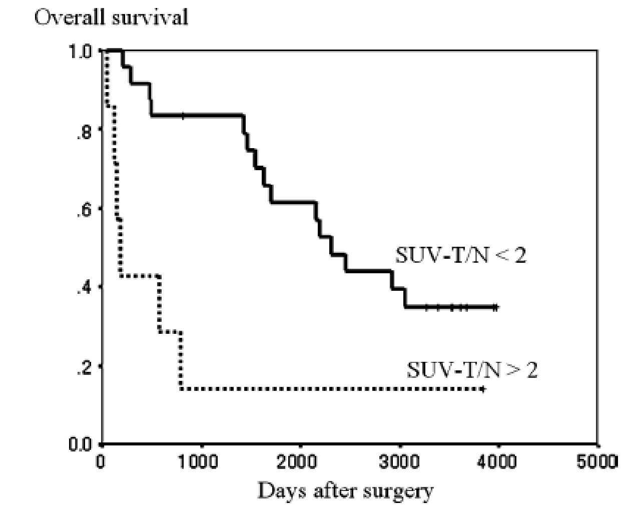
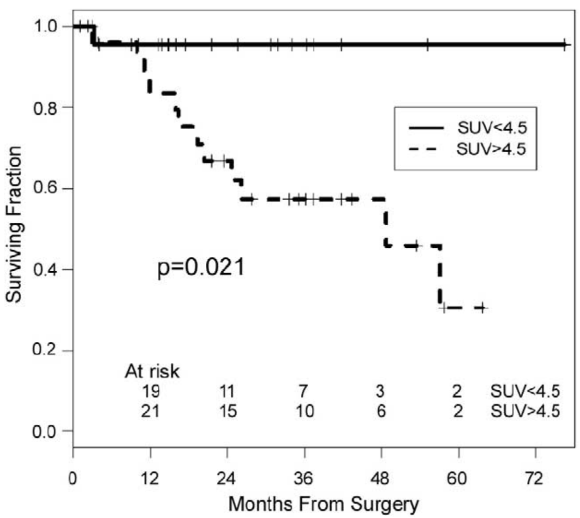
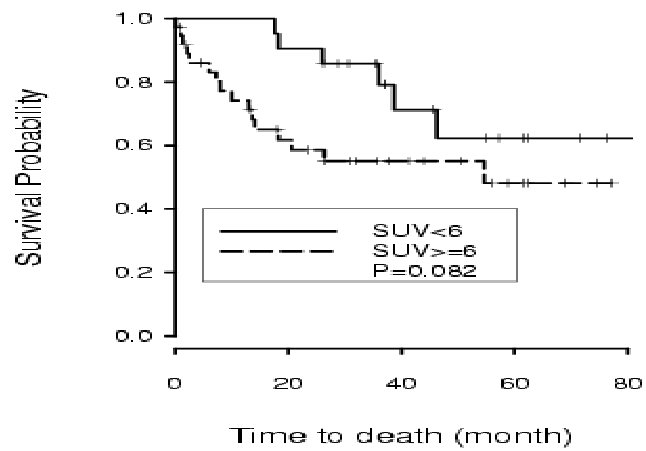


Figure 1. Survival curves of patients with SUV ratio >2 (8 patients; *broken line*) or <2 (23 patients; *solid line*).

HCC- World J Surg, 2006



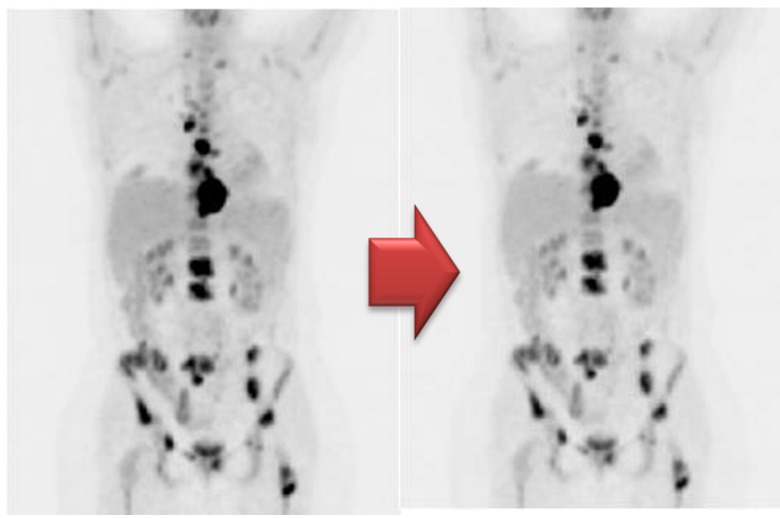
Esôfago Ann Thorac Surg, 2006



Pulmão Proc Am Thorac Soc 2009

PET FDG

Monitorização Terapêutica

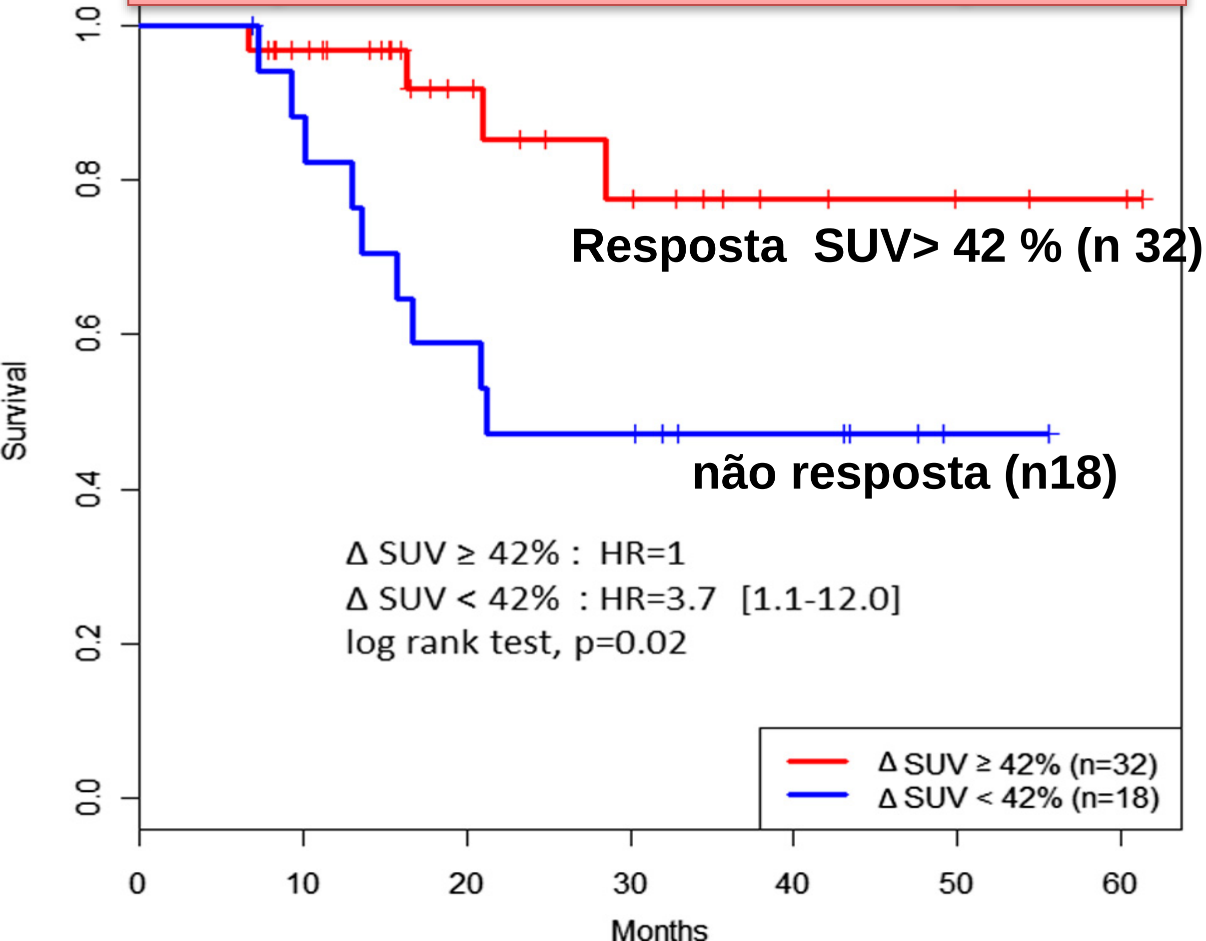


Resposta completa – Parcial -- Progressão/novas lesões

PET FDG em CA de mama

Monitorização Terapêutica

FDG pós 2 ciclos QT neo em 50 pts



pCR 59%

3-year EFS 78%

pCR 0%

3-year EFS 47%

Groheux D, E J Cancer 2014

Glicólise aeróbia

Fenótipo comum à maioria dos TUs, diferentes mecanismos

Epifenômeno OU

Fator necessário ?

Hipóxia ←→ HIF1-a ←→ glicólise

- Hipóxia e acidose selecionam células resistentes à apoptose
- pH ácido associado a invasão (degradação matriz extracelular?)

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Gillies, JNM 2008

CANCER → PROGNOSTICO e CONDUTA

1. Origem

1. Tipo histológico

2. Estadiamento

↓

considera também:

– Condições clinicas
– Idade e sexo
– Histologia
– **Marcadores moleculares → FDG**

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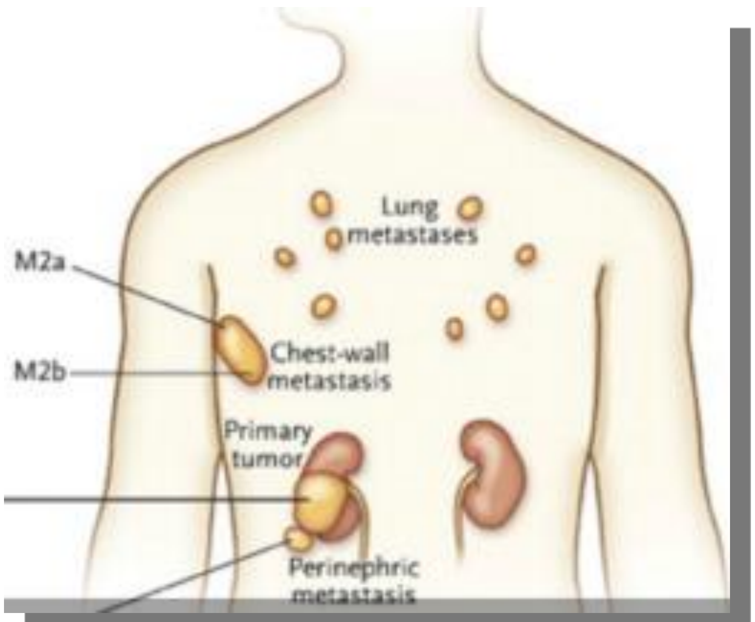
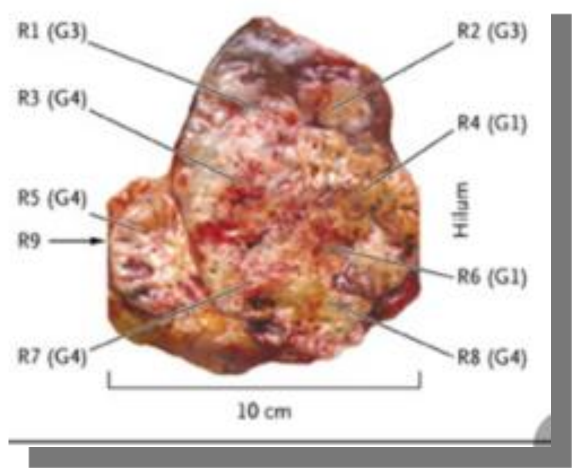
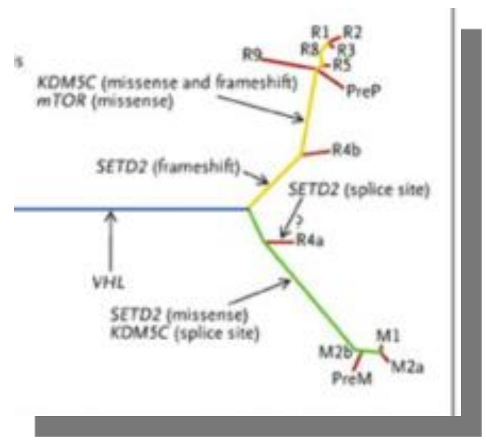
Marcadores moleculares
vs
Heterogeneidade tumoral

Dificuldade de estabelecer perfil genético e molecular por biópsia:







Gerlinger Intratumor heterogeneity NEJM 2012

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Imagem molecular no câncer

Uso de métodos de imagem *in vivo* para visibilização, caracterização e quantificação de processos biológicos normais ou patológicos em nível celular e molecular

- Compreensão de mecanismos fisiopatológicos
- Diagnóstico e prognóstico
- Predição ou avaliação de resposta a drogas alvo
- Desenvolvimento de novos tratamentos

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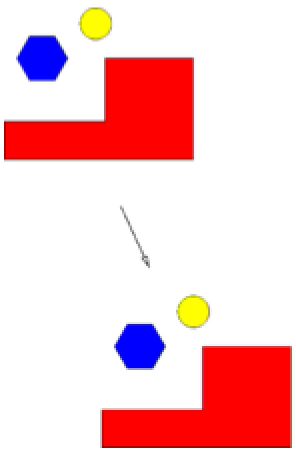
Pesquisa Translacional



Pré-clínico

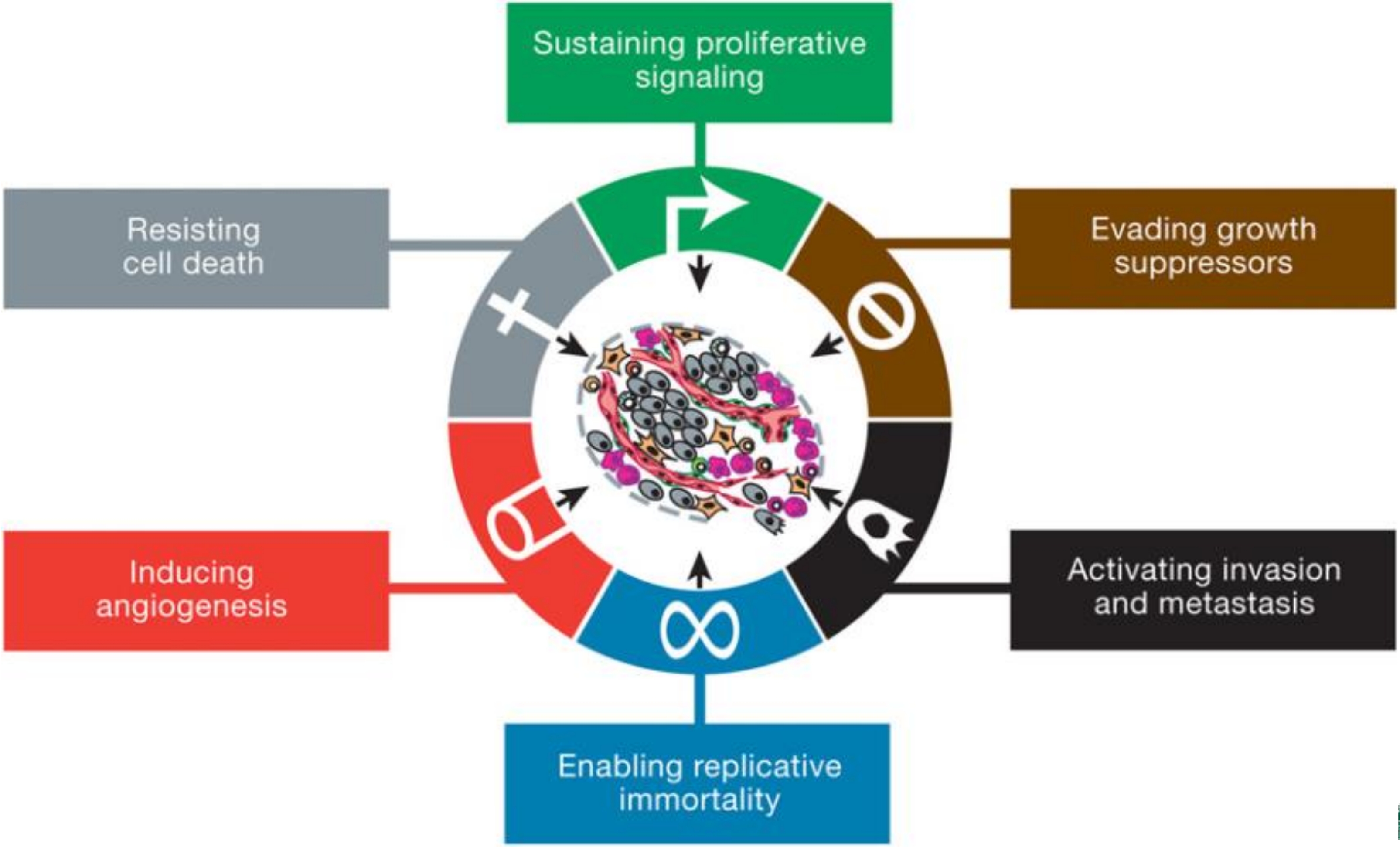
- Identificação de alvo molecular
- Desenvolvimento de ligante (radiofármaco)
- Avaliação experimental / pré-clínica

Clínico

- Imagem em seres humanos
- Aprovação por órgãos reguladores
- Aplicação clínica

Hallmarks of cancer – 2000

Hanahan & Weinberg



Hanahan & Weinberg
Cell **2011**

Reprogramação do metabolismo energético

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Imagem molecular
...além do FDG

Radionuclídeos

^{82}Rb

^{11}C

^{68}Ga

^{18}F

^{64}Cu

^{124}I

Vallabhajosula
Semin Nucl Med 2011

Radiofármacos

[^{18}F]Florbetapir (AV-45)

^{18}F-AV-45
[^{18}F]Flutemetamol
^{18}F-3′-FPIB
[^{18}F]Florbetaben (AV-1)
^{18}F-BMS747158

[^{18}F]FP-DTBZ (AV-133)

[^{18}F]FACBC (Fluciclovine)
[^{18}F]BAY 85-8050
[^{18}F]Fluciclatide

^{124}I-Girentuximab, or G250 (Redectane)
^{18}F-Sodium fluoride

3′-^{18}F-FLT

[^{18}F]FMISO

^{64}Cu-ATSM

Imagem molecular
...além do FDG

• Proliferação:	^{18}F-fluorotimidina (FLT)
• Membrana:	^{11}C-colina / ^{18}F-colina
• Síntese proteica :	^{11}C-metionina
• Hipóxia:	^{18}F-FMISO e ^{18}F-FAZA
• Angiogênese	RGD
• Receptor hormonal:	^{18}F-fluoroestradiol (FES)
• Outros receptores:	somatostatina, PSMA

^{18}F-FLT

DNA: A-**T** C-G (RNA: A-**U** C-G)

metanálise correlaciona com Ki-67

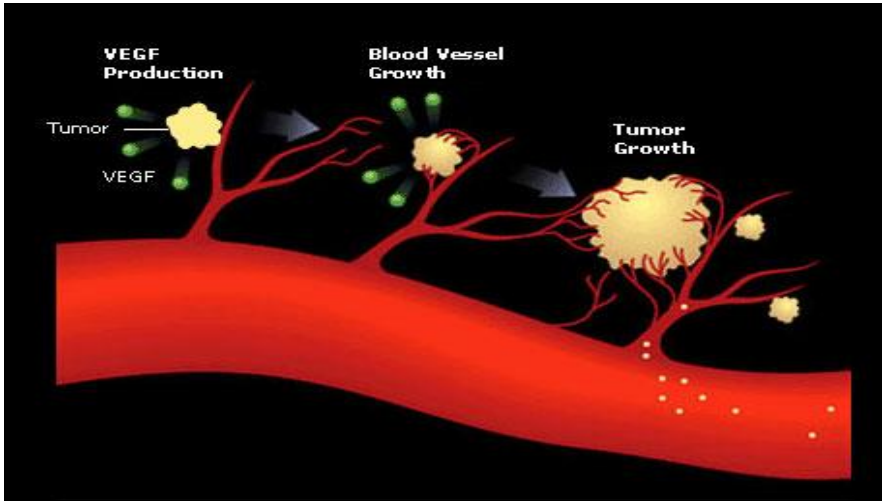
avaliação de atividade proliferativa

Chalkidou 2012

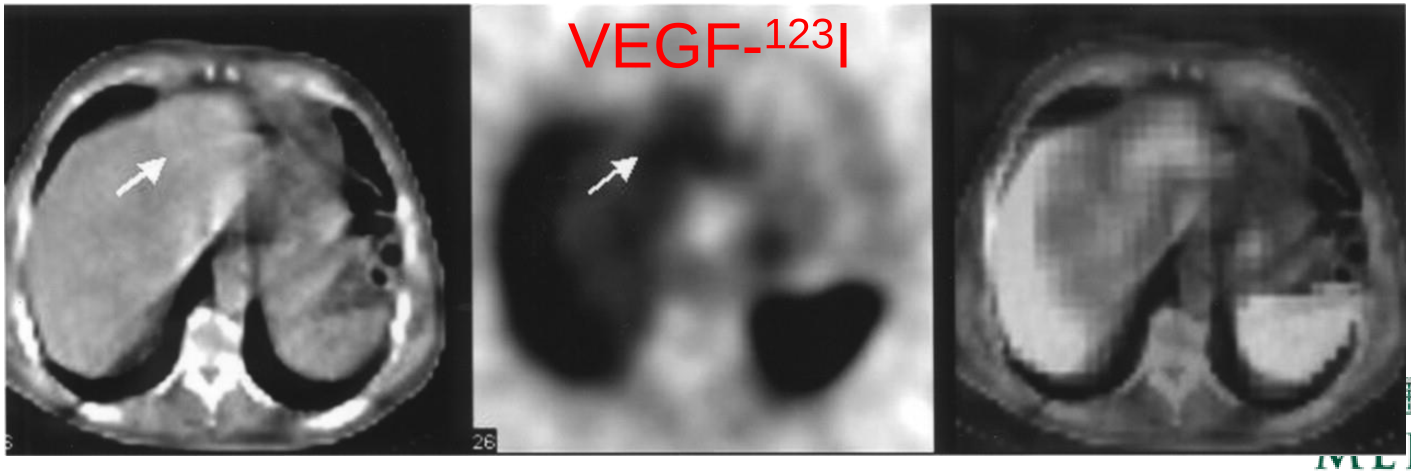
Angiogênese

VEGF - fator de crescimento endotelial vascular

αvß3 Integrina = peptídeos–RGD marcados com ^{99m}Tc, ^{18}F e ^{111}In)



McQuade QJNM 2003



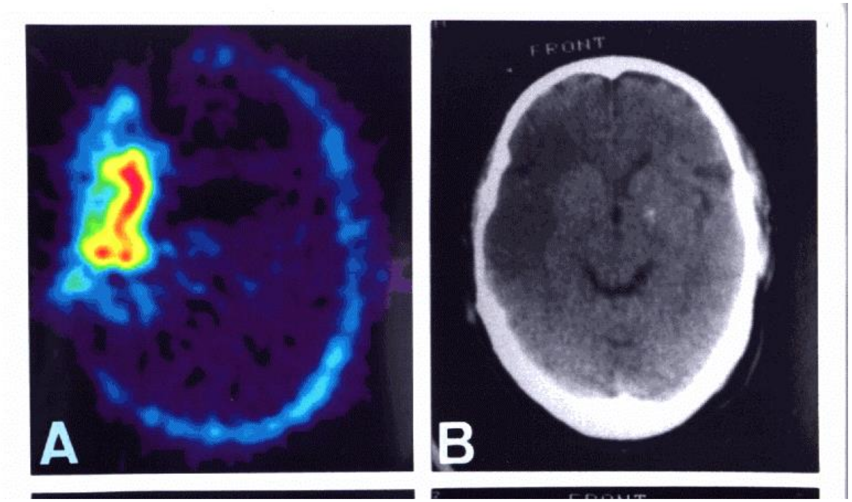
Li S. *Annals of Oncology, 2003*

Hipóxia

Determina resistência tumoral a QT e RT

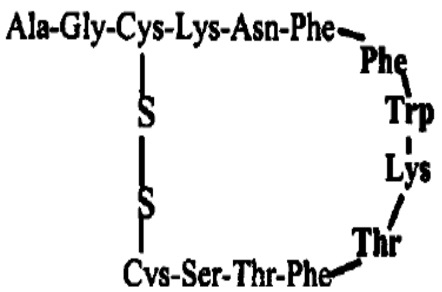
nitroimidazólicos (ex:^{18}FMISO)

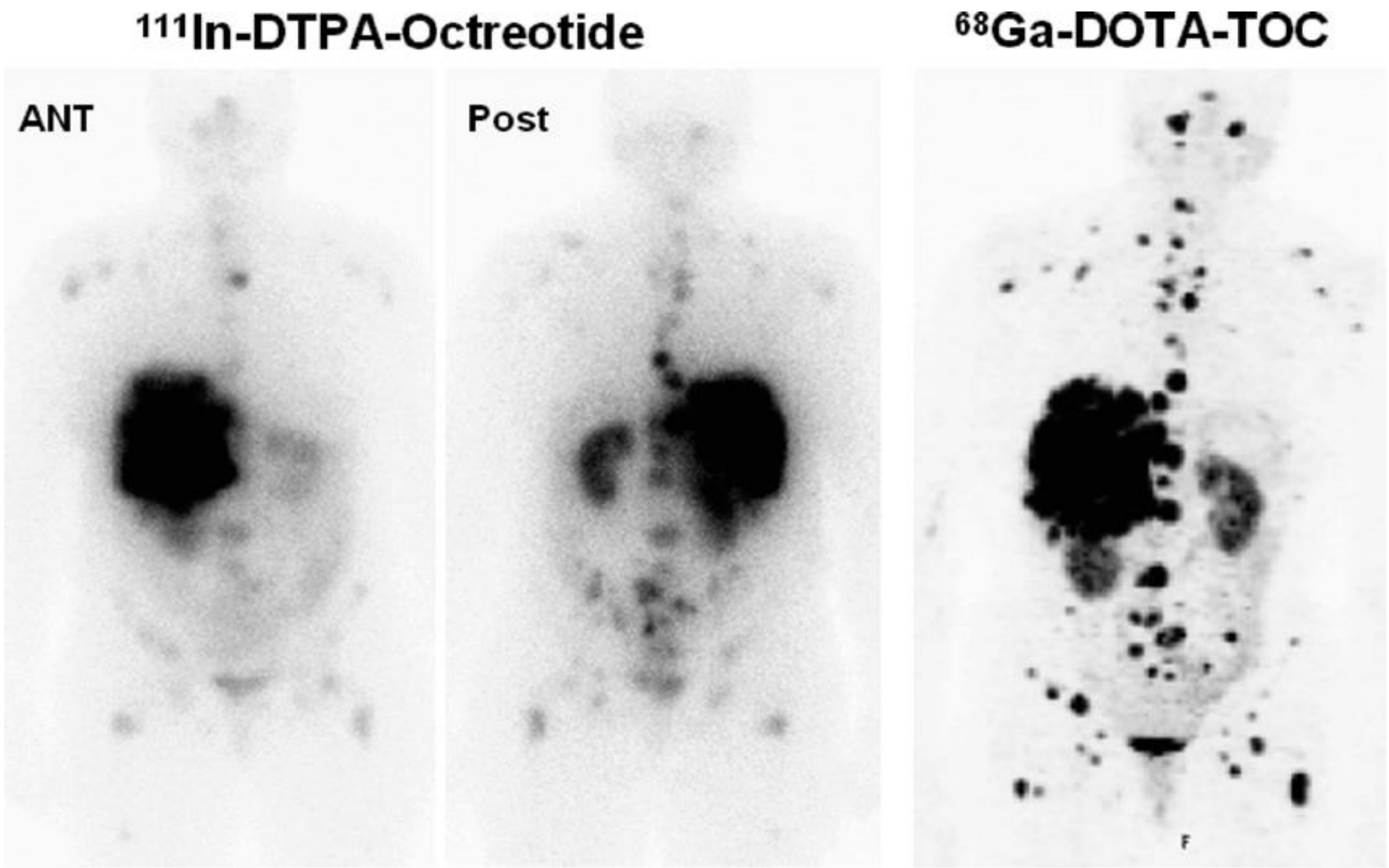
- redução do grupo nitro (NO_2)
- revertidos em pO_2 normal e persistentes em hipóxia



Wu LC (http://npcc.vghtpe.gov.tw/pet-5year/clinical/penum.htm)

Peptídeos





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Obrigado !

mtsapienza@hotmail.com