Nuclear Medicine

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Nuclear Medicine 101

• A radioactive atom is produced in a nuclear reactor (fission, neutron enrichment) or cyclotron (using protons, deuterons or alpha particles)

• This radioactive atom is coupled to a carrier molecule in most cases

• The radioactive compound is administered to patients (intravenous, orally, intradermal, inhaled)
A brief history of Nuclear Medicine

- **1930s:** Discovery of artificial isotopes, notably Iodine-131 and Tc99m
- **First treatment in 1939 with phosphorus-32**
- **First treatment with iodine-131 in 1946**
- **Gamma camera (Anger) and Rectilinear Scanner (Cassen) in 1950s**
- **Thyroid imaging 1950-1960**
- **Liver/spleen scanning, bone imaging, brain tumour localization 1960-1970s**
- **Positron emission tomography in 1970s+ for brain imaging**
- **Cardiac imaging 1980s+**
- **Cancer imaging in the 1990s and beyond**
Some definitions

• **SPECT**: Single photon emission computed tomography
  – Three dimensional images acquired from the single photon emission produced by gamma emission decay
  – Typical isotopes: Tc-99m, In-111, TI-201, I-123,…

• **PET**: Positron emission tomography
  – Three dimensional images acquired from the dual photon emission produced by the annihilation of a positron
  – Typical isotopes: C-11, F-18, Ga-68, O-15, Rb-82, …
Technetium-99m, the medical isotope of the 20th century

- Element 43 discovered by Carlo Perrier and Emilio Segrè in 1936
- Technetium-99 discovered by Seaborg and Segrè at the Berkeley Radiation Laboratory
- BNL, 1950s: Tucker and Green developed the first $^{99}\text{Mo}/^{99m}\text{Tc}$ generator
- BNL, 1960: Powell Richards, presented the first paper on the generator.
- Richards met with Paul Harper on the flight to Rome and spent the flight “extolling the merits of $^{99m}\text{Tc}$”

In part from http://www.bnl.gov/bnlweb/history/Tc-99m.asp
Single photon emitters in Oncology

- **$^{99m}$Tc MDP Bone Scan**
- **$^{99m}$Tc Sulfur Colloid**
  - Sentinel Node Detection
- **$^{99m}$Tc Sestamibi**
  - Breast Cancer Detection
- **$^{111}$In Pentetretotide** for neuroendocrine cancers
How many tests are done in Nuclear Medicine?

- 30,000 diagnostic tests per week using radiopharmaceuticals
- 30,000-40,000 tests per day in USA
- 80-90% use technetium-99m
PET imaging 101
Cancer Imaging Targets BCCA/TRIUMF

G-coupled receptors:
- GRPR (prostate, breast) $^{18}$F, $^{68}$Ga-PEG-Bombesin derivatives
- NPY Y1 (breast, prostate, neuroblastoma) $^{18}$F-BVD-16
- SST-2 (neuroendocrine, breast) $^{68}$Ga-DOTA-TOC
- BKRB1 (prostate, breast) $^{18}$F-, $^{68}$Ga-BKRB1 antagonists

Amino Acid Transport:
- $^{18}$F DOPA
- Others

Tyrosine Kinase Receptors:
- HER2 and variants:
  - $^{89}$Zr-Antibodies

Membrane Synthesis:
- $^{11}$C-choline

Protein Synthesis:
- $^{11}$C Methionine

mRNA Imaging:
- CPP-PNA

Proliferation/Thymidine Transport:
- $^{18}$F-Fluorothymidine

Enzymes:
- CA IX

Neovascularisation:
- $^{68}$Ga-RGD-Dimers

Hormone receptors:
- $^{18}$F-Fluoroestradiol
Molecular imaging: beyond imaging the structure

- Traditional imaging methods use differences in organ morphology, appearance to make a diagnosis.
- Functional imaging methods use radioisotopes and contrast agents to look at organ function.
- Molecular imaging methods use specific probes (usually radioactive) to measure biochemical processes and proteins.
Example: Glucose metabolism

- Many oncogene pathways increase glycolysis by cancer cells (particularly PI3K/Akt pathway)
- Utilization of glucose increases markedly
- $^{18}$F-FDG (Fluorodeoxyglucose) is a glucose analogue that is trapped in cancer cells in proportion to glucose utilization
- Discovered in a US government laboratory
- Used in cancer diagnosis worldwide
Staging Cancer with PET/CT
Response to experimental drugs

Baseline

1 month after onset of therapy
Imaging hormone receptors

• “Receptors” are proteins expressed in cells to which a hormone or drug will bind
• Estrogen receptors are expressed in 80% of breast cancer and stimulate cancer growth
• The pathologist will look for these receptors when examining a biopsy
• What happens when the cancer spreads elsewhere?
Measuring response to hormone therapy

Baseline

After 2 months (aromatase inhibitor)
Are tumours all the same within a given patient?

Proven inguinal breast cancer metastases, some with increased FDG uptake but no FES uptake (arrow). 18F-FDG PET scan, top row; 18F-FES PET scan, bottom row.
Canadian Cyclotron Infrastructure

• 18 Cyclotrons in Canada in 11 facilities
  – 6 in Vancouver
  – 2 each in Hamilton, Toronto, Montreal
  – 1 in Edmonton, Winnipeg, London (ON), Ottawa, Sherbrooke, Halifax

• 7 new cyclotrons planned or purchased
  – Edmonton, Saskatoon, Toronto, Thunder Bay, Montreal, Sherbrooke, St-John

Worldwide: Over 350 cyclotrons in 2006
Unplanned shutdown of NRU reactor extended

Chalk River, 2009 May 18 — Atomic Energy of Canada Limited (AECL) reported on Friday, May 15th that the NRU reactor was safely shut down on Thursday, May 14th due to a loss of electrical power that occurred in parts of eastern Ontario and western Quebec.

During routine monitoring in the early morning hours of May 15th, a small leak of heavy water was detected within the NRU reactor facility. The leak rate is estimated to be at about 5 kg/hr. The heavy water is fully contained and is being stored in specially designed drums.

The location of the heavy water leak has been identified at the base of the reactor vessel in a location where there is corrosion on the outside wall of the vessel. Repair options are currently under consideration and activities are being planned. As a result, AECL anticipates that the NRU reactor will remain out of service for more than one month.

Chalk River repairs have $70-million price tag: AECL

52-year-old reactor has been plagued by shutdowns in recent years

Steve Rennie
Ottawa — The Canadian Press
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Atomic Energy of Canada Ltd. has put a $70-million price tag on repairing its downed Chalk River reactor.
Can Cyclotrons help prevent isotope shortages?

- Distribution model established for $^{18}$F-Fluorodeoxyglucose (110 min half-life)
- Mixed model possible for $^{18}$F (1 h irradiation) and $^{99m}$Tc production (3-6 h irradiations)
- Take advantage of existing infrastructure
- Proof of concept established in 1971 (Beaver and Hupf)
Challenges for cyclotron production of Tc99m

- Calculate theoretical yields
- Target Preparation
- Designing new targets for existing cyclotrons
- Technetium extraction/isolation
- \(^{100}\)Mo recycling
- Assess impact on patient dosimetry
- Assess practical usable yields
Impact of other Tc Radioisotopes on Patient Absorbed Dose

Theoretical dosimetry estimations for radioisotopes produced by proton-induced reactions

Figure 3. The per cent difference between the total effective doses following the injections of sestamibi labeled with technetium produced in a cyclotron (mixture-Tc) and obtained from the reactor produced generator. Cyclotron production corresponded to 6 h irradiation of a thick target A (left) and target C (right) with proton beams. Doses resulting from target thicknesses leading to beam energy degradation from 16-, 19-, 24–10 MeV and from 16-, 19-, 24–6 MeV are compared for injection periods varying from 0 h–24 h after EOB. Dark color column bars represent the dose differences for beam energy decreasing to 6 MeV, while the light color bars are for the energy decreasing to 10 MeV.

Additionally, radiation-absorbed doses to specific organs were calculated for 6 h irradiations by a 200 µA proton beam with the energy 19–10 MeV on enriched targets A and C. Table 5 shows the per cent dose difference between radiopharmaceuticals labeled with mixture-Tc produced in a cyclotron when irradiating the enriched target A, and labeled with pure $^{99m}$Tc obtained from a generator. Table 6 shows similar results for the enriched target C. The ratio of absorbed doses corresponding to injection periods varying between 0 and 24 h is compared. Additionally, the same data are presented in figure 4, where the per cent differences in radiation doses to organs with the most significant uptake after injection with technetium labeled sestamibi, phosphonates and pertechnetate at 0–24 h after EOB is shown. The dashed lines in the figures represent the per cent dose differences using enriched targets A (97.39% enrichment), while the solid lines represent the per cent dose differences using target C (99.01% enrichment).

Other Cyclotron Isotopes of Interest

- $^{89}$Zr ($t_{1/2}$ 78.4 h), to label proteins and antibodies
- $^{68}$Ga ($t_{1/2}$ 68.3 min) and $^{44}$Sc ($t_{1/2}$ 3.93 h), the technetium replacements of the future?
- $^{94m}$Tc ($t_{1/2}$ 53 min), the positron emitting technetium
- $^{86}$Y ($t_{1/2}$ 14.74 h), a diagnostic counterpart to $^{90}$Y used in therapy
- $^{11}$C ($t_{1/2}$ 20.4 min), if only there was a cyclotron in every hospital!

Can all be produced by small cyclotrons < 10 MeV
Conclusion

• Cyclotrons provide us with medical isotopes that play a critical role in:
  – Understanding Cancer Biology
  – Diagnosis and Staging of Cancer
  – Monitoring response and Personalizing the treatment approach

• A large number of existing cyclotrons are capable of securing Tc99m supply

• Many other useful isotopes can be produced by small medical cyclotrons
Thank You!

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• Collaborators:

• Staff and Students:

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