Radiation Carcinogenesis, hereditary effects of Radiation & effects on the fetus



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Overview

- Biological response to radiation
- Radiation induced genetic damage
- Effects of Radiation exposure
- Stochastic vs. deterministic effects
- Exposure to radiation
- Radiation & the fetus
- Conclusions

The various responses

- Adaptive response: the cells adapt after a lower initial dose of radiation; effect of a further dose is modified
- Genomic instability: mutations or change in gene expression levels due to radiation
- Bystander effect: possible communication between the irradiated cell & non-irradiated cells triggering cellular & molecular changes

Relationship between biological responses to radiation



Radiation-induced changes in gene expression



Wyrobek

Adaptive Response

When a small dose of radiation is given before a larger one, it would be expected there would be more chromosome aberrations than when just the large dose was given. But that is not what happens. With a small "tickle" dose before the larger dose, there were only about half as many aberrations than with just a large dose!



Radiation-induced Genetic Damage



Genomic Instability



There is a need for a change in interpreting radiation biology

- Adaptive response and protective effects vs detrimental effects
- Hit theory vs. bystander effects
- Mutation vs. gene induction
- Single cell vs tissue responses

- High doses of radiation can produce cancer
- Radiation is a good cell killer
- Radiation is a poor mutagen/carcinogen
- Low doses of radiation produce different cell and molecular responses than high doses (Protective vs harmful?)
- Linear extrapolation of risk is conservative

Effects of Radiation Exposure



Stochastic Effects

- These are primarily of two types:
 - Carcinogenesis
 - Hereditary effects
- Both have:
 - A **random** nature of appearance.
 - No threshold dose for appearance.
 - Definite **latent period** for appearance after exposure.
 - Probablity of induction **increases** with the dose received.
 - Severity of the effect is **independent** of the dose received.

Types of exposure

- 2 types of exposure have been defined :
 - Normal exposures
 - Potential exposures
- Humans can be exposed to radiation while:
 - Pursuing their normal occupation (Occupational exposure)
 - Undergoing some medical or dental procedures for diagnosis or evaluation (Medical exposure)
 - During normal daily life (Public exposure)

Occupational Exposures

• Occupational exposure which is defined as all exposures of workers incurred in the course of their work

Medical Exposures

- Medical exposure which is defined as exposure incurred:
 - By patients as part of their own medical or dental diagnosis or treatment
 - By persons, other than those occupationally exposed, knowingly while voluntarily helping in the support and comfort of patients
 - By volunteers in a programme of biomedical research involving their exposure.
- Three broad classes:
 - Patients
 - Caregivers
 - Medical test subjects

Public Exposure

• **Public exposure**, which is defined as exposure incurred by members of the public from radiation sources,

Excludes any occupational or medical exposure and the normal local natural background radiation

Equivalent Dose

- The SI unit for equivalent dose is joules/kg or sievert
- One Sievert = 100 rem (radiation equivalent man)

• Radiation Weighting factor is a somewhat arbitrarily chosen conservative value based on a range of RBEs related to the linear energy transfer (LET) of the radiation.

Radiation Weighting Factors

Radiation Type	Weighting Factor
Photons all energies	1
Electrons all energies	1
Protons, other than fission fragments, energy more than 2 MeV	5
Neutrons energy < 10 KeV	5
10 KeV to 100 KeV	10
100 KeV to 2 MeV	20
> 2 MeV to 20 MeV	10
> 20 MeV	5
Alpha particles, fission fragments, heavy nuclei	20

1) Quality factors for various radiation types; Source: ICRP publication 60

2) Excludes Auger electrons

3) All values relate to radiation incident on the body for external radiation and for internal sources, emitted from the source

Tissue Weighting Factors

Tissue / Organ	Tissue Weight 1990	Weight 2007
Gonads	0.2	0.08
Stomach	0.12	0.12
Colon	0.12	0.12
Lung	0.12	0.12
Red Bone Mar	row 0.12	0.12
Breast	0.05	0.12
Remainder	0.05	0.12
Thyroid	0.05	0.04
Esophagus	0.05	0.04
Bladder	0.05	0.04
Liver	0.05	0.04
Bone Surface	0.01	0.01
Skin	0.01	0.01
Brain		0.01
Salivary glands	S	0.01

Modern Day Levels: ICRP

	Occupational exposure	Exposure to apprentices 16–18 years of age	Public exposure
Effective dose (whole body) (mSv)	20, averaged over five consecutive years 50 in a single year ^a	6	1, averaged over five consecutive years 5 in a single year ^b
Equivalent dose (eye lens) (mSv)	150	50	15
Equivalent dose (hands, feet, skin) (mSv)	500	150	50

 Provided that the average effective dose over five consecutive years does not exceed 2 mSv/a.

^b Provided that the average effective dose over five consecutive years does not exceed 1 mSv/a.

The maximum effective dose for occupational exposure is **50 mSv** in **1 year** and the **total exposure** for **5 years** should not exceed **100 mSv** (avg 20 mSv).

Foetal effects of radiation

- Thousands of pregnant women are exposed to ionising radiation each year
- Lack of knowledge is responsible for great anxiety and probably unnecessary termination of pregnancies
- For most patients, radiation exposure is medically appropriate and the radiation risk to the fetus is minimal

Example: justified use of CT

Pregnant female, was in motor vehicle accident



3 minute CT exam and taken to the operating room. She and the child survived



Fetal radiation risk

- There are radiation-related risks throughout pregnancy that are related to the stage of pregnancy and absorbed dose
- Radiation risks are most significant during organogenesis and in the early fetal period, somewhat less in the 2nd trimester, and least in the 3rd trimester











• Deterministic effects of ionising radiation for in-utero irradiation are

- Death
- Malformation
- Growth retardation
- Abnormal brain development leading to severe mental retardation

Radiation-induced malformations

- Malformations have a threshold of 100-200 mGy or higher and are typically associated with central nervous system problems
- Fetal doses of 100 mGy are not reached even with 3 pelvic CT scans or 20 conventional diagnostic x-ray examinations
- These levels can be reached with fluoroscopically guided interventional procedures of the pelvis and with radiotherapy

Central nervous system effects

- During 8-25 weeks post-conception the CNS is particularly sensitive to radiation
- Fetal doses in excess of 100 mGy can result in some reduction of IQ (intelligence quotient)
- Fetal doses in the range of 1000 mGy can result in severe mental retardation and microcephaly, particularly during 8-15 weeks and to a lesser extent at 16-25 weeks

Heterotopic gray matter (arrows) near the ventricles in a mentally retarded individual occurring as a result of high dose in-utero radiation exposure



Frequency of microcephaly as a function of dose and gestational age occurring as a result of in-utero exposure in atomic bomb survivors (Miller 1976)



Leukaemia and cancer...

- Radiation has been shown to increase the risk for leukaemia and many types of cancer in children
- The cancer risk is more for the exposure in 3-4 weeks old pregnancy. After 3-4 weeks of preganancy the risk is believed to be fairly in dependent of stage of pregnancy

Leukaemia and cancer (cont'd)

- The relative risk may be as high as 1.4 (40% increase over normal incidence) due to a fetal dose of 10 mGy
- For an individual exposed in utero to 10 mGy, the absolute risk of cancer at ages 0-15 is about 1 excess cancer death per 1,700

Pre-conception irradiation

- Pre-conception irradiation of either parent's gonads has not been shown to result in increased risk of cancer or malformations in children
- This statement is from comprehensive studies of atomic bomb survivors as well as studies of patients who had been treated with radiotherapy when they were children

- A missed period in a regularly menstruating woman should be considered due to pregnancy, until proven otherwise
- Notices regarding pregnancy should be posted in patient waiting areas, such as

"If it is possible that you might be pregnant, notify the physician or other staff before your xray examination, treatment, or before being injected with a radioactive material"

Approximate fetal doses from conventional xray examinations

Data from the UK, 1998

Examination	Mean (mGy)	Maximum (mGy)
Abdomen	1.4	4.2
Chest	<0.01	<0.01
Intravenous uro- gram; lumbar spine	1.7	10
Pelvis	1.1	4

Approximate fetal doses from fluoroscopic and computed tomography procedures

Data from the UK, 1998

Examination	Mean (mGy)	Maximum (mGy)
Barium meal (UGI)	1.1	5.8
Barium enema	6.8	24
Head CT	<0.005	<0.005
Chest CT	0.06	1.0
Abdomen CT	8.0	49

Higher dose procedures

- Radiation therapy and interventional fluoroscopically-guided procedures may give fetal doses in the range of 10-100 mGy or more depending on the specifics of the procedure
- After such higher dose medical procedures have been performed on pregnant patients, fetal dose and potential fetal risk should be estimated by a knowledgeable person

Nuclear medicine and pregnant patients...

- Most diagnostic procedures are done with shortlived radionuclides (such as technetium-99^m) that do not cause large fetal doses
- Often, fetal dose can be reduced through maternal hydration and encouraging voiding of urine
- Some radionuclides do cross the placenta and can pose fetal risks (such as iodine-131)

Nuclear medicine and pregnant patient (cont'd)

- The fetal thyroid accumulates iodine after about 10 weeks gestational age
- High fetal thyroid doses from radioiodine can result in permanent hypothyroidism
- If pregnancy is discovered within 12 h of radioiodine administration, prompt oral administration of stable potassium iodine (60-130 mg) to the mother can reduce fetal thyroid dose. This may need to be repeated several times

Approximate whole body fetal dose (mGy) from common nuclear medicine procedures

Procedure	Activity (MBq)	Early pregnancy	9 months
Tc-99 ^m Bone scan Lung scan	750 240 300 400	4.7 0.9 0.6 4.4	1.8 0.9 1.1 3.7
Liver colloid scan Thyroid scan Renal DTPA Red blood cell	300 930	9.0 6.0	3.5 2.5

Research on pregnant patients

Research involving radiation exposure of pregnant patients should be discouraged



Radiation exposure of pregnant workers

- Pregnant medical radiation workers may work in a radiation environment as long as there is reasonable assurance that the fetal dose can be kept below 1 mGy during the pregnancy
- 1 mGy is approximately the dose that all persons receive annually from penetrating natural background radiation

Termination of pregnancy...

- High fetal doses (100-1000 mGy) during late pregnancy are not likely to result in malformations or birth defects since all the organs have been formed
- A fetal dose of 100 mGy has a small individual risk of radiation-induced cancer. There is over a 99% chance that the exposed fetus will NOT develop childhood cancer or leukaemia

Termination of pregnancy (cont'd)

- Termination of pregnancy at fetal doses of less than 100 mGy is NOT justified based upon radiation risk
- At fetal doses in excess of 500 mGy, there can be significant fetal damage, the magnitude and type of which is a function of dose and stage of pregnancy
- At fetal doses between 100 and 500 mGy, decisions should be based upon individual circumstances

Risks in a pregnant population *not* exposed to radiation

Risks:

- Spontaneous abortion > 15%
- Incidence of genetic abnormalities 4-10%
- Intrauterine growth retardation 4%
- Incidence of major malformation 2-4%

- Any dose in diagnostic procedures which doubles the childhood cancer risk with respect to natural rate should be avoided if there is no serious detrimental effect of not doing the diagnostic procedure
- Even if such examination is carried out and the risk of cancer is still low in absolute terms (below 1 in 200 and mostly it is below 1 in 1000), termination of pregnancy is not justified solely on the basis of radiation risk to unborn child

Conclusions

- Radiation has a profound effect on the genetic make up of cells
- The results are varied & depend upon the cell type irradiated & dose level
- Various theories for the biological effects of radiation have been propounded
- Radiation exposure of the fetus: fetal age & radiation dose levels both matter
- Guidelines should be followed; medical termination of pregnancy is rarely justified



THANK YOU