Basic Nuclear Engineering 4
(原子核工学基礎第四)
(5) Therapeutic Use of Radiation

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1. Overview of cancer radiotherapy

Characteristics of Cancer Radiotherapy

◆Merits

①Can preserve the function or shape
(Better QOL, quality of life)

②Can treat cancer anywhere, even if it is not accessible in operation.

③Has less burden to body than operation
– Can be applied to patients with complication or elderly patients

◆Demerits

①Sometimes local control rate is lower than operation

②Sometimes incur radiation damages (adverse events) in surrounding tissues

がん放射線治療の特徴

◆長所

①機能、形態の温存が可能(QOL, quality of life)

②いかなる場所でも(手術のできない場所でも)
　治療可能

③手術に比べて負担が小さい
　合併症を有する患者、高齢者にも適用可能

◆短所

①手術に比べ、局所制御で劣る場合もあり

②周辺組織の放射線障害(有害事象)

Objectives of Radiotherapy

①Radical radiotherapy
Aim to cure cancer completely by radiation.

②Palliative radiotherapy (Alleviate symptoms)
Not expect complete cure of cancer but aim the improvement of QOL.
Ex) Alleviate pain and prevent fracture in bone metastasis
Improve neuronal symptom in brain metastasis
Improve achalasia (esophageal motility disorder) in advanced esophagus cancer, etc.

③Preventional radiation
Aim to prevent metastasis or recurrence
Ex) Lymph node irradiation after breast cancer operation
Whole brain irradiation after cure of leukemia, etc.

放射線治療の目的

①根治的照射
　放射線による癌の治癒を目的とする。

②姑息的(症状緩和)照射
　根治は期待できないが、患者のQOLの向上を目的として行う。
　例）骨転移に対する疼痛の緩和と病的骨折の防止
　　　脳転移に対する神経症上の改善
　　　進行食道癌に対する通過障害の改善　など

③予防的照射
　転移、再発などの予防を目的とする。
　例）乳癌手術後の領域リンパ節照射
　　　白血病における寛解後の全脳照射　など

Methods of Radiotherapy

◆External irradiation

Irradiate from outside of body

Stationary beam irradiation and moving beam irradiation.

◆Brachytherapy (Using small radiation source)

Insert radioactive substance to cancer tissue (tissue irradiation)

Insert it to the nearby cavity (intracavity irradiation)

Press it as embedded in a mold against cancer tissue

(mold irradiation/prosthetic irradiation)

放射線治療の方法

◆外部照射
　体の外から放射線を照射する。
　放射線ビームを固定して照射する固定照射と
　放射線ビームを動かしながら照射する運動照射がある。

◆小線源治療
　放射性物質を癌病巣内に刺入したり(組織内照射)、
　近傍の体腔内に挿入したり(腔内照射)、
　モールドに包埋して病巣部に密着させたり
　(補綴装置(モールド)照射)する。

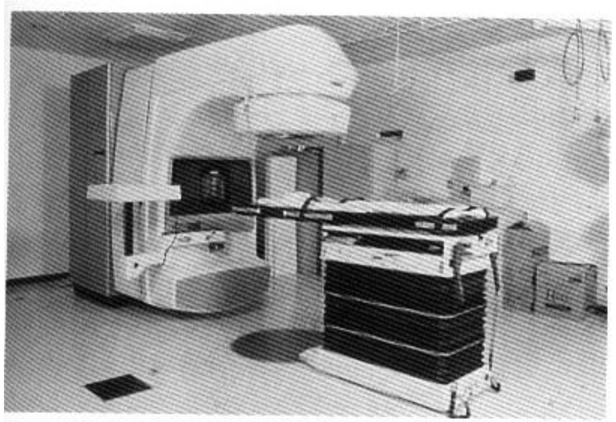
External Irradiation Apparatus

◆Tele-cobalt irradiator

^{60}Co emits γ-ray of 1.17 MeV and 1.33 MeV, which is one of the highest energy among γ-ray. However, the energy is lower than high energy X-ray and, thus, less penetrative. It is suitable for cancers located near body surface, like head and neck cancer and breast cancer. Radiation source needs to be renewed every 5-6 years, as the half life of ^{60}Co is 5.2 years.

◆High energy accelerator

Accelerate electron. In addition to electron itself, X-ray can be also used. Linear accelerator, LINAC is most common.



LINAC装置(「放射線医科学」より)

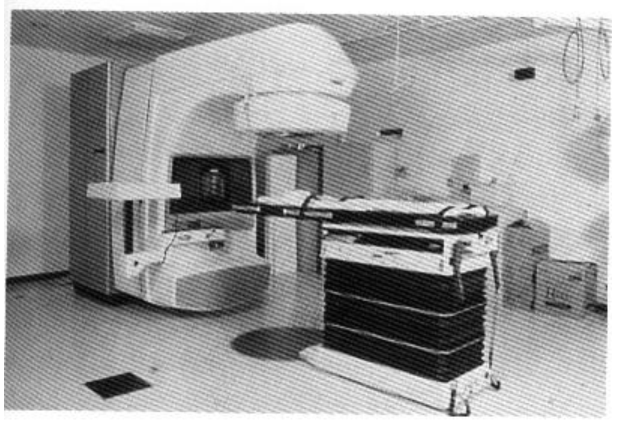
外部照射装置

◆コバルト遠隔照射装置

^{60}Co線源から放出される1.17MeVと1.33MeVのγ線を照射する。
γ線としては最もエネルギーが高いものの一つであるが、
高エネルギーX線よりはエネルギーが低く、深部到達性に
やや劣るため、頭頸部腫瘍や乳癌などそれほど深部ではない
病変に適している。
^{60}Coの半減期は5.2年であるため、5～6年に一度線源の交換が
必要。

◆高エネルギー加速装置

線形加速器ライナック(LINAC)が代表的。
いずれも電子を加速する装置。
加速電子の他、電子がターゲットに
当たって発生するX線が利用できる。



LINAC装置(「放射線医科学」より)

Intensity Modulated Radiation Therapy (IMRT)

Use high energy X-ray generated by LINAC.
Dose distribution fit to the tumor volume is achieved by computer-controlled movement of radiation source and multi-leaf collimeters.

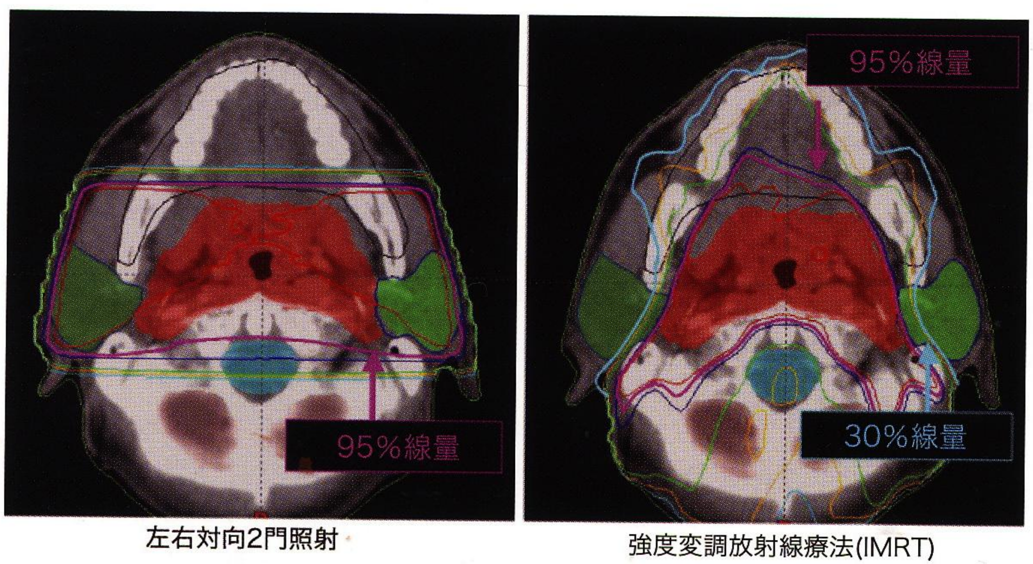


図 3.8.2　上咽頭腫瘍に対する線量分布の比較

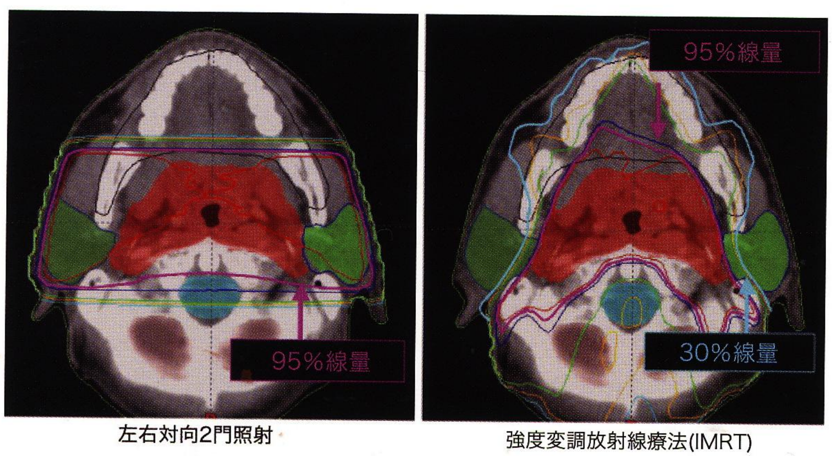
左右対向 2 門照射では，病巣部と耳下腺にほぼ同じ線量（95% 以上）が照射されている．IMRT では，病巣部（赤色）には 95% 以上が照射されるが，耳下腺（緑色）は 30% 以下の線量に低く抑えられている．

（「放射線医科学」より）

強度変調治療(IMRT)

(Intensity Modulated Radiation Therapy)

LINACから発生する高エネルギーX線を利用。
照射ヘッドに内蔵されているマルチリーフ・コリメータを精密に制御することにより、照射野内での放射線強度を自在に調節。
これを多方向から照射することにより、標的となる腫瘍に線量を集中し、周辺正常組織への線量を最小化する。



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（「放射線医科学」より）

2. Oxygen effect and hypoxic cells (酸素効果と低酸素細胞)

Oxygen effect

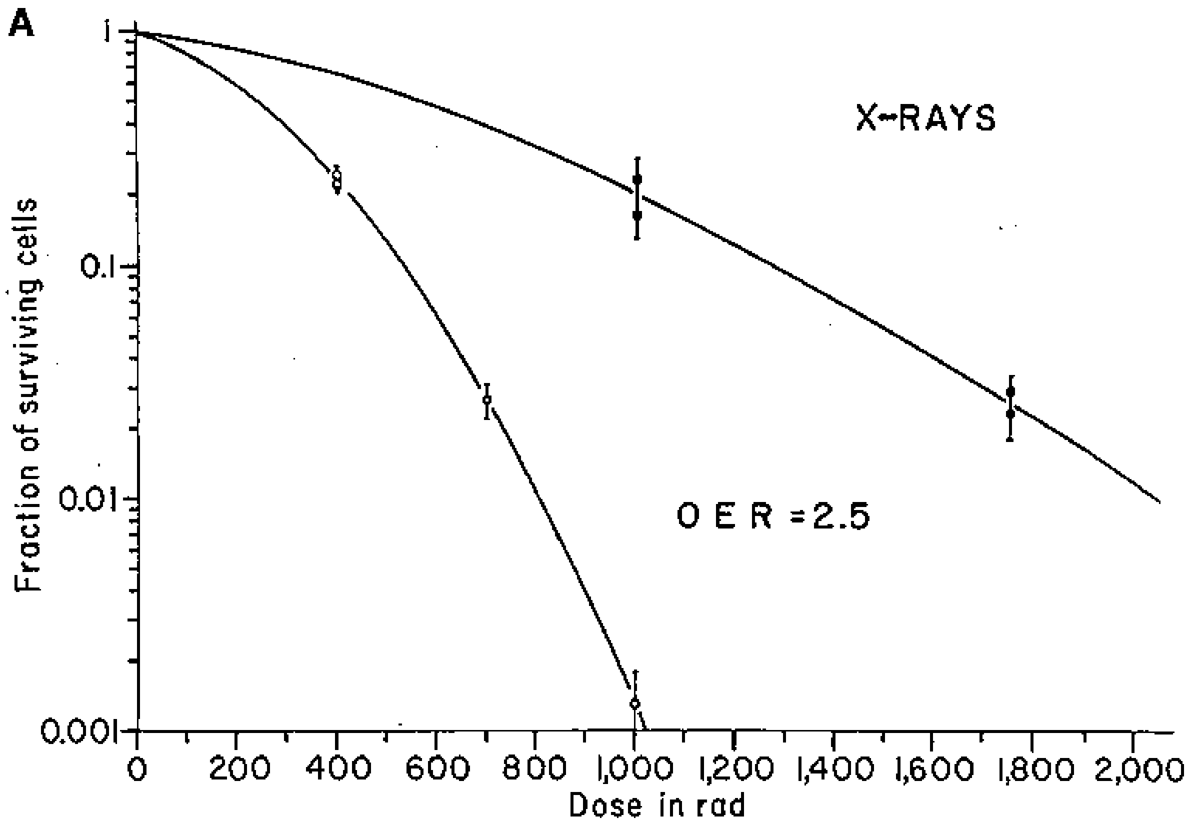
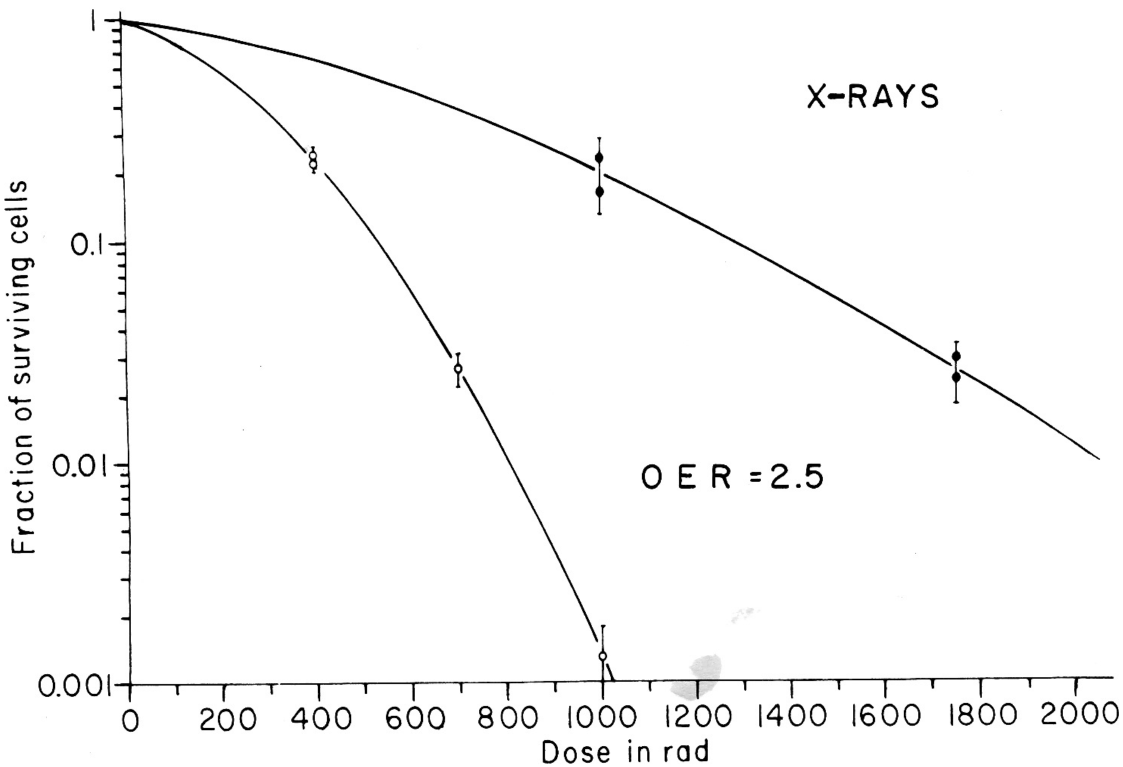


FIGURE 6.2 ● The oxygen enhancement ratio (OER) for various types of radiation. The OER for low-energy α-particles is unity (**C**). X-rays exhibit a larger OER of 2.5 (**A**). Neutrons (15-MeV $d^{+} \rightarrow T$) are between these extremes, with an OER of 1.6 (**B**). (Adapted from Barendsen GW, Koot CJ, van Kersen GR, Bewley DK, Field SB, Parnell CJ: The effect of oxygen on impairment of the proliferative capacity of human cells in culture by ionizing radiations of different LET. *Int J Radiat Biol Relat Stud Phys Chem Med* 10:317–327, 1966; and Broerse JJ, Barendsen GW, van Kersen GR: Survival of cultured human cells after irradiation with fast neutrons of different energies in hypoxic and oxygenated conditions. *Int J Radiat Biol Relat Stud Phys Chem Med* 13:559–572, 1968, with permission.)

酸素効果

酸素に富んだ状態では、欠乏状態に比べて
生物効果が大きくなる



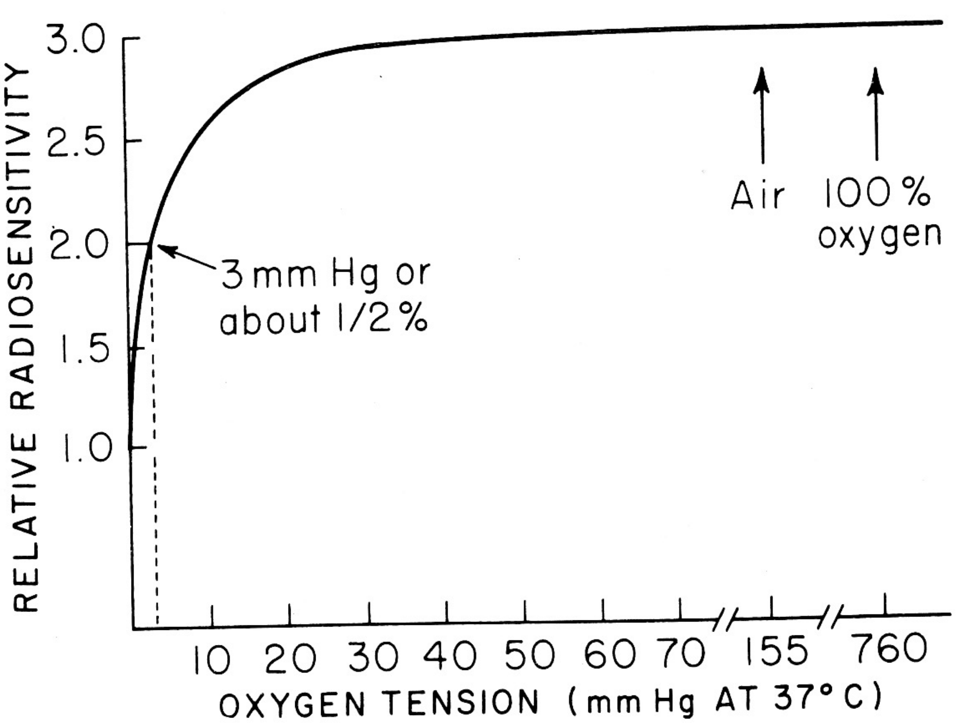
OER(Oxygen Enhancement Ratio)

$$\text{OER} = \frac{\text{A dose required to obtain a certain effect under anoxic condition}}{\text{A dose required to obtain the same effect under oxic condition}}$$

OER(Oxygen Enhancement Ratio; 酸素増感比)

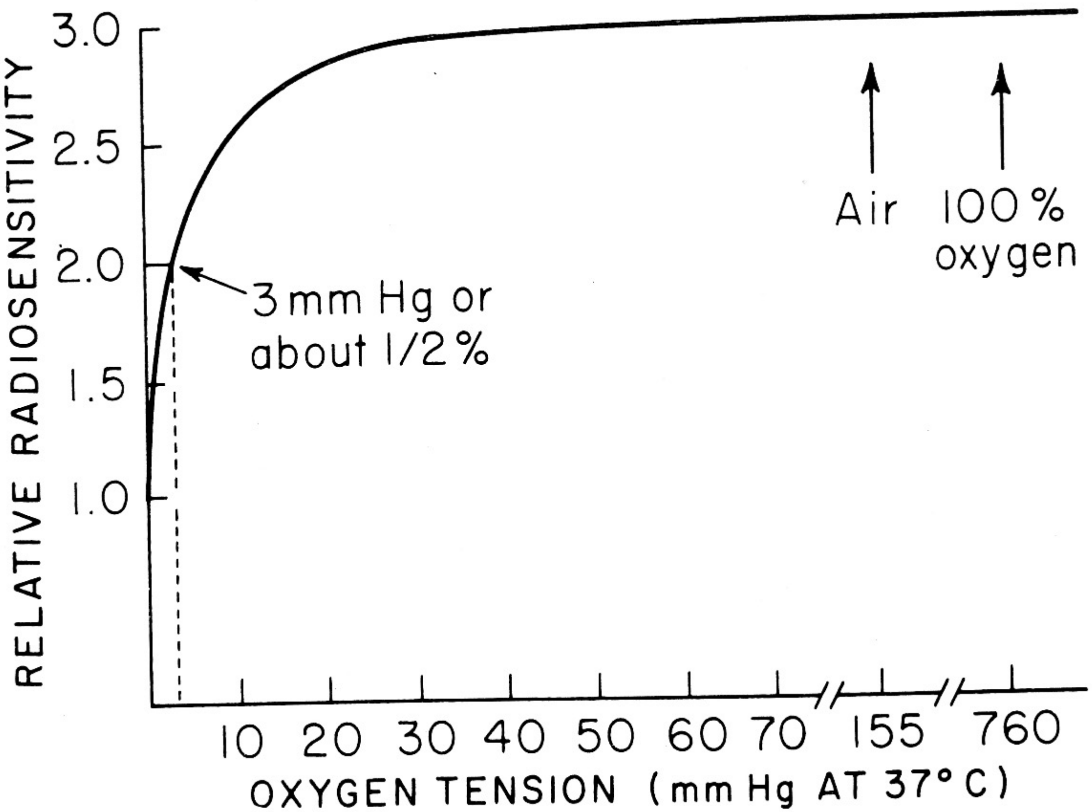
$$\mathrm{OER} = \frac{\text{酸素欠乏条件下である生物効果を得るのに必要な線量}}{\text{酸素が富んだ状態で同じ生物効果を得るのに必要な線量}}$$

Oxygen effect as a function of oxygen concentration



The oxygen effect reaches plateau at 2%.
It does not mean that the effect becomes larger by increasing the oxygen concentration to 100%.

酸素分圧とOER



酸素濃度が2%になると大気下とほぼ同じ
100%まで増やしても生物効果は増強されない

Possible mechanism of oxygen effect

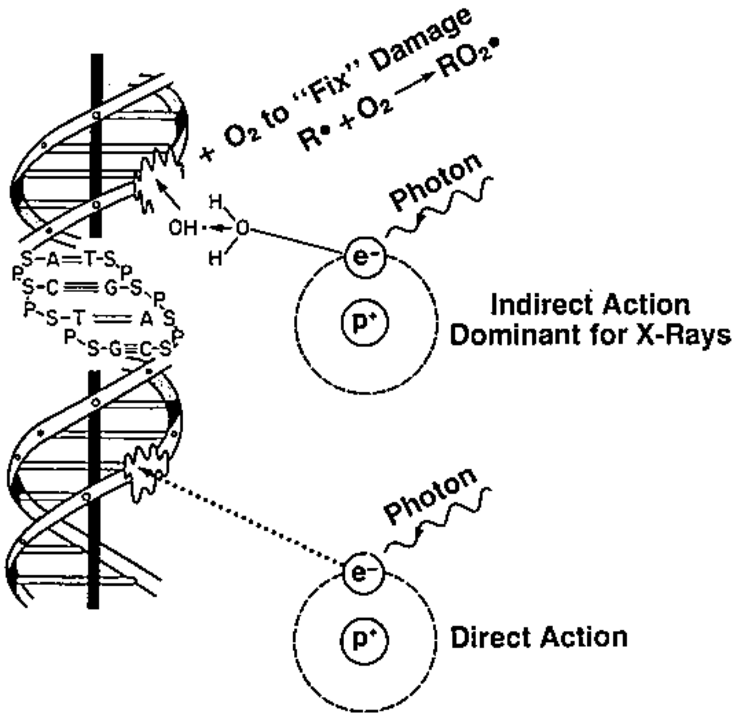
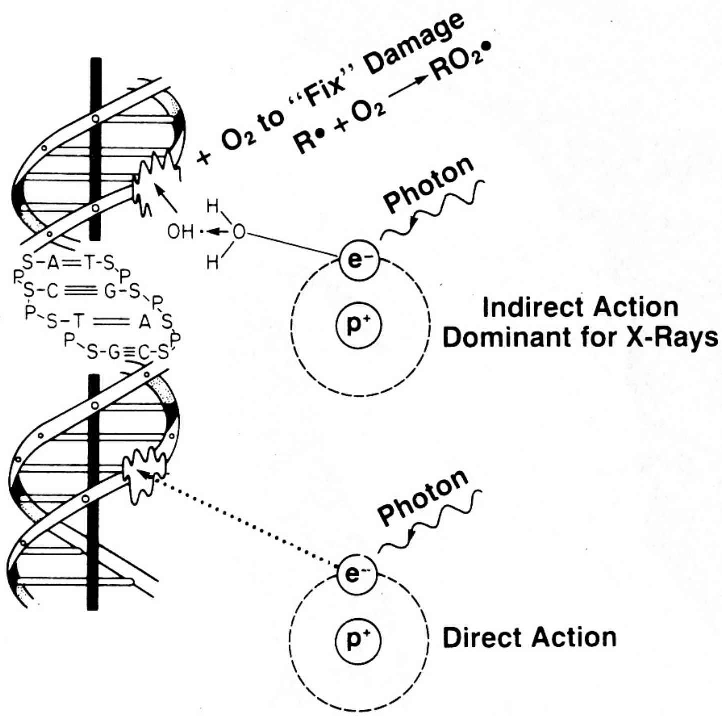


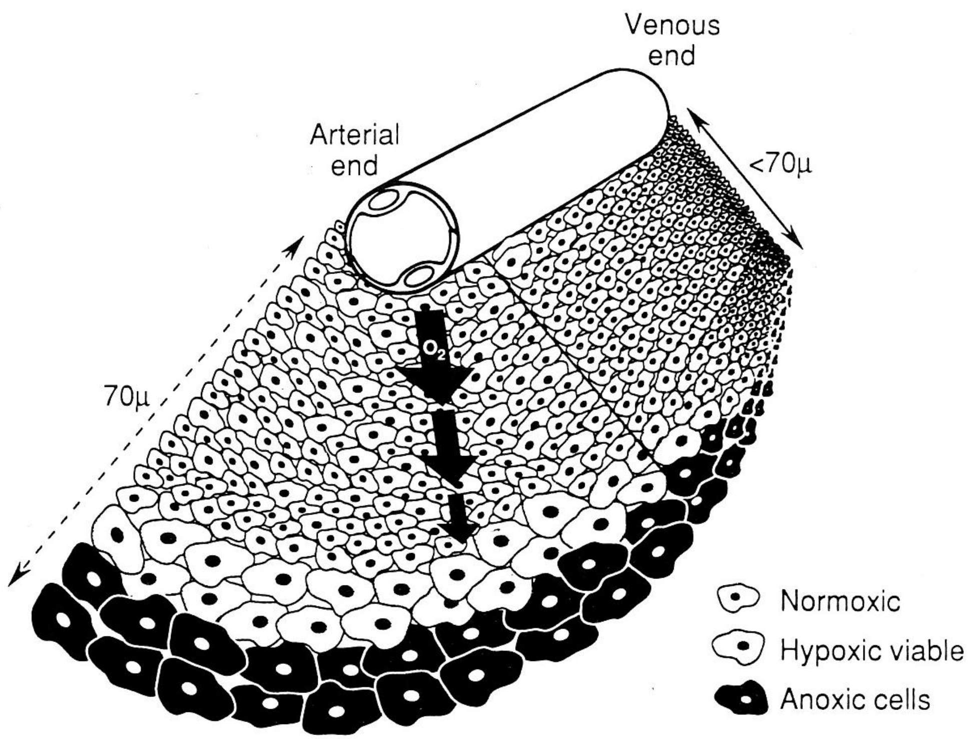
FIGURE 6.3 ● The oxygen fixation hypothesis. About two thirds of the biologic damage produced by x-rays is by indirect action mediated by free radicals. The damage produced by free radicals in DNA can be repaired under hypoxia but may be "fixed" (made permanent and irreparable) if molecular oxygen is available.

酸素効果が現れる仕組み―1つの仮説



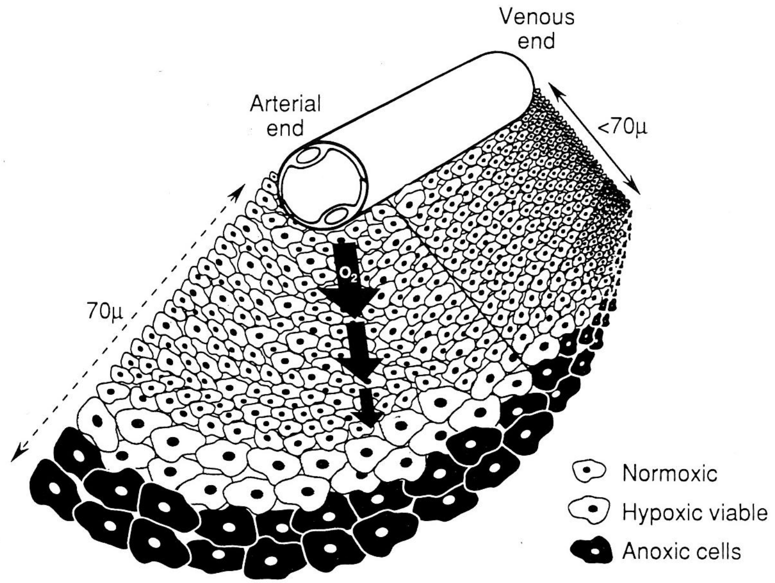
放射線の生体分子(DNA)への作用には直接効果と間接効果がある。
酸素は、間接効果、即ち、ラジカルがDNAに作用してできた損傷と反応して、修復されにくい型にする。
(損傷の固定)

Hypoxic cells in tumor



In the tumor tissue, the proliferation is so rapid that the angiogenesis cannot follow. Then, cells distant from the blood vessel become deficient in oxygen and nutrition.

腫瘍における低酸素細胞(Hypoxic cell)



増殖が速い腫瘍では、血管新生が追いつかない場合がある。
血管から離れた細胞は酸素欠乏状態になる。従って、腫瘍には
(1)血管に近く、十分な酸素供給を受け、活発に増殖する細胞
(2)血管から離れて、著しい酸素欠乏のため、死に至る細胞
そして、その中間に
(3)生存はできるが、酸素濃度が低い細胞　が存在する。

Hypoxic cells in tumor

There are some cells,which is deficient in oxygen supply but is still alive

↓

Such cells are radioresistant due to oxygen effect

↓

Toward the improvement of radiotherapy,

1) Development of hypoxic cell sensitizer,
2) Measurement of oxgen concentration and imaging of hypoxic cells
3) Dose fractionation condition to facilitate “reoxygenation” of hypoxic cells.

are awaited.

酸素効果：酸素に富んだ状態では、欠乏状態
　　　　　に比べて生物効果が大きくなる

↓

低酸素細胞は放射線抵抗性

↓

放射線治療向上のために
１）低酸素細胞増感剤の開発
２）酸素分圧測定と低酸素細胞可視化
３）再酸素化を促す時間的線量分布

3. LET and RBE

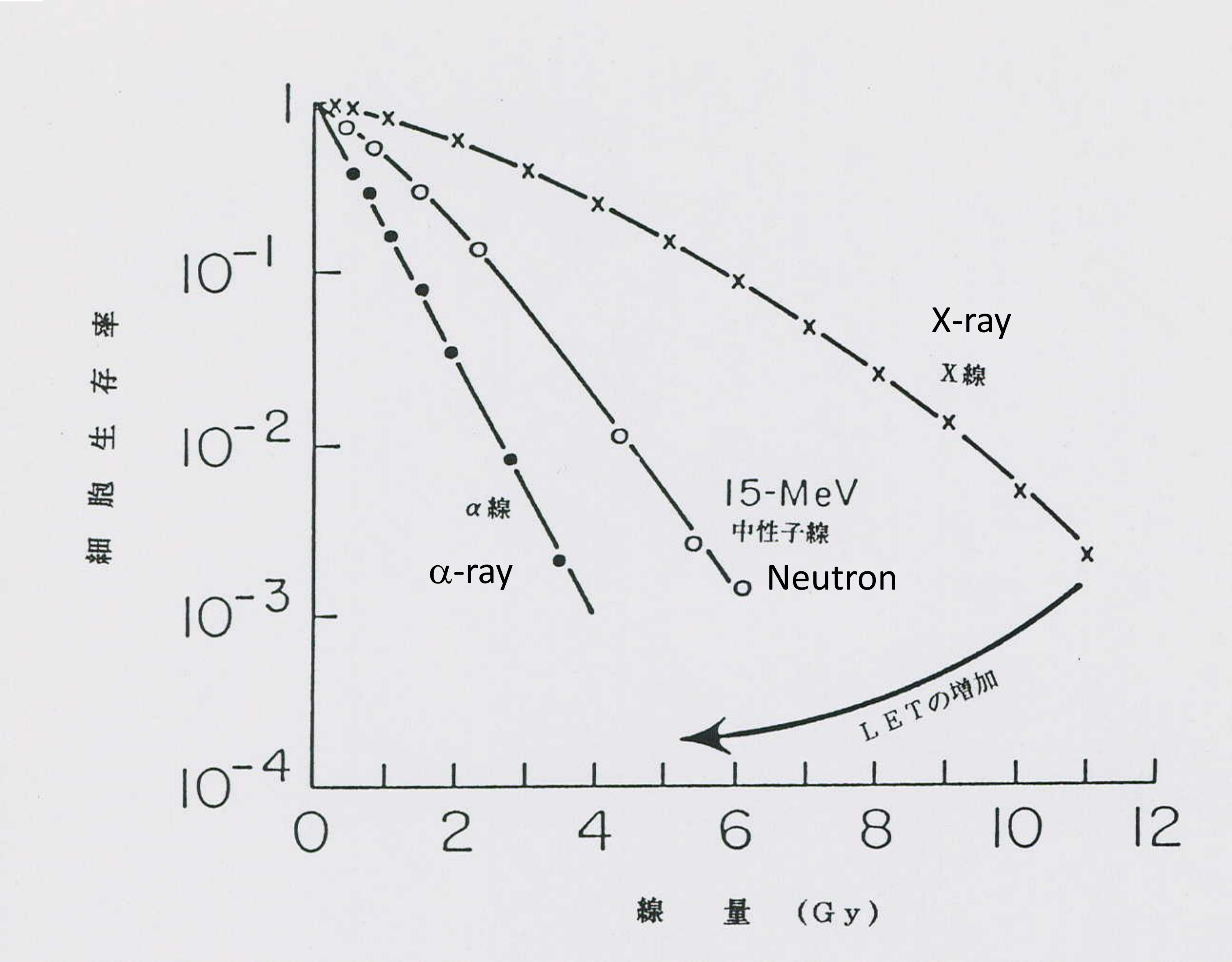
LET (Linear Energy Transfer)

Energy deposited per unit length

Unit：keV/μm

Radiation		LET (keV/μm)
Photon	^{60}Co γ-ray	0.2
	250KV X-ray	2.0
Proton	10MeV	4.7
	150MeV	0.5
14MeV　Neutron		12 (track average) 100 (energy average)
2.5MeV α-ray		166
2GeV Fe ion		1,000

Cell survival curves for different types of radiation



RBE(Relative Biological Effectiveness; 生物学的効果比)

$$\mathrm{RBE}=\frac{\text{ある生物効果を起こすのに必要な基準放射線の吸収線量(Gy)}}{\text{同じ生物効果を起こすのに必要な着目放射線の吸収線量(Gy)}}$$

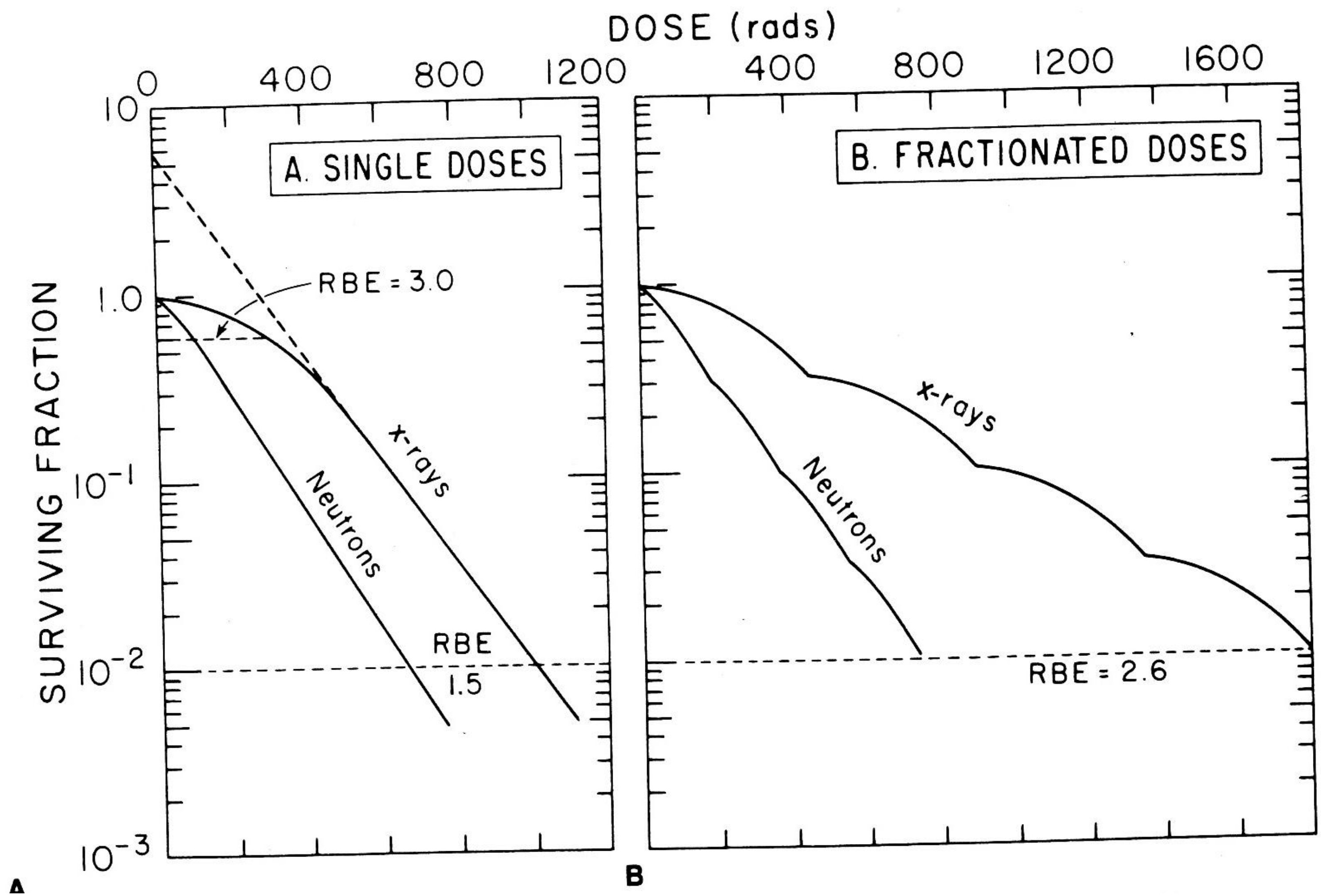
基準放射線：250kVのX線を用いる場合が多い

RBE (Relative Biological Effectiveness)

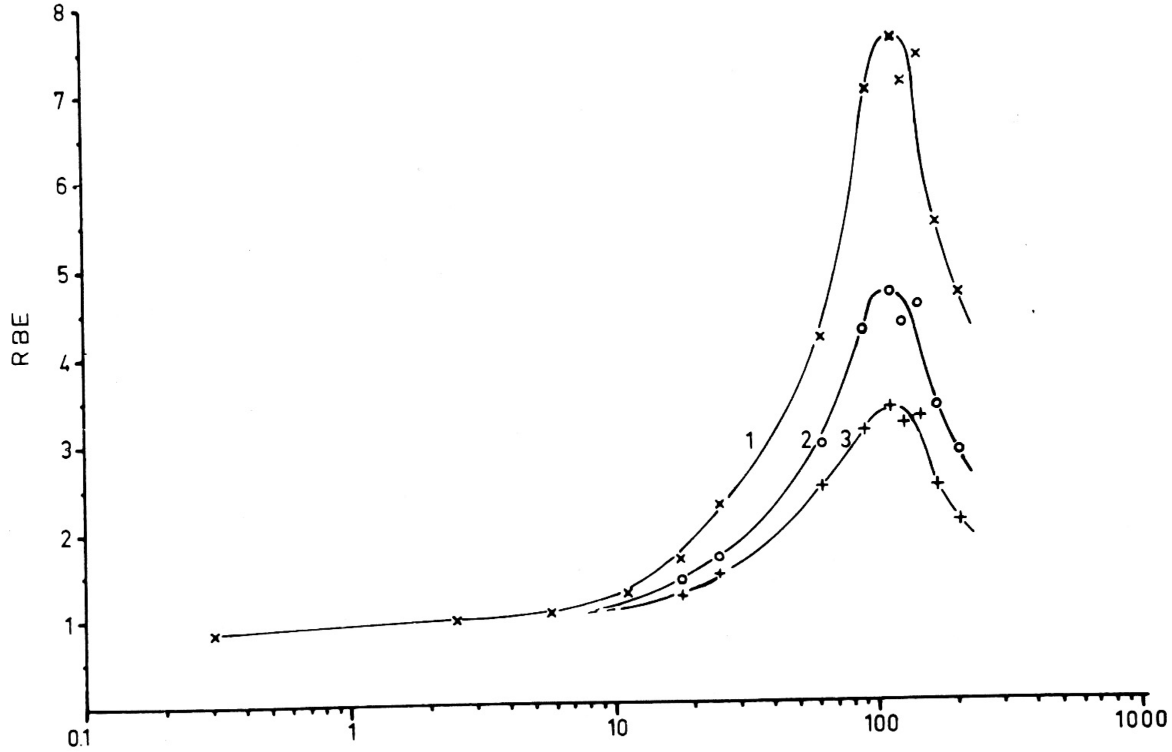
$$\text{RBE} = \frac{\text{Absorbed dose of standard radiation to induce some biological effect(Gy)}}{\text{Absorbed dose of radiation of interest to induce the same biological effect (Gy)}}$$

Standard radiation: 250kV X-ray is usually used

RBE depends on type and extent of biological effect and also on endpoint and fractionation

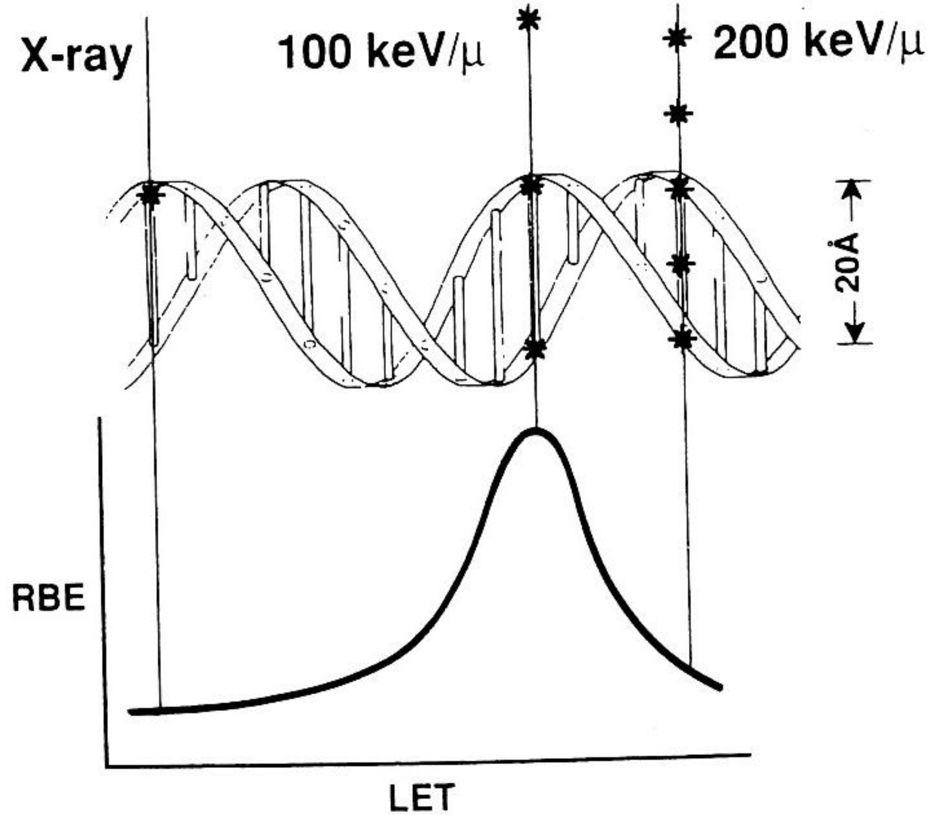


Relationship between LET and RBE



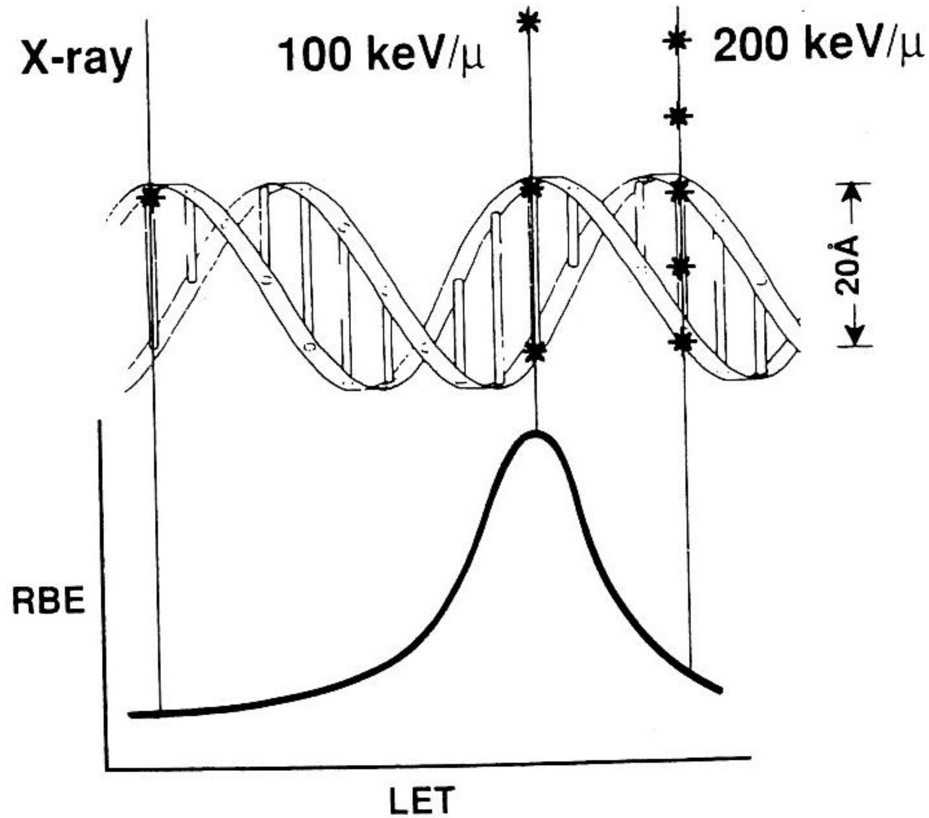
RBE increases with LET but decreases at extremely high LET

Why there is a peak of LET?



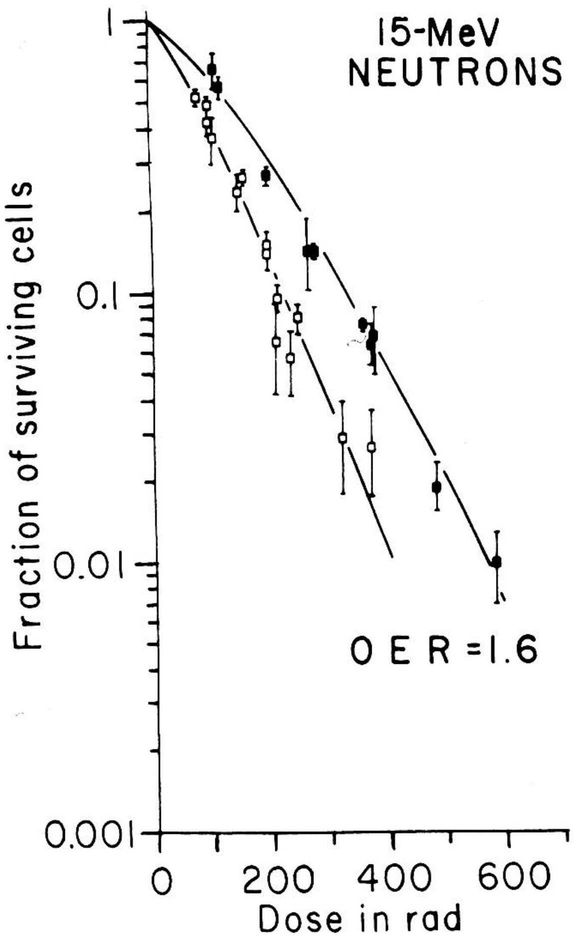
At low LET, the ionization is spatially sparse and DSB not generated efficiently. However, in extremely high LET, there are excess ionization as the dose increases (Overkilling hypothesis).

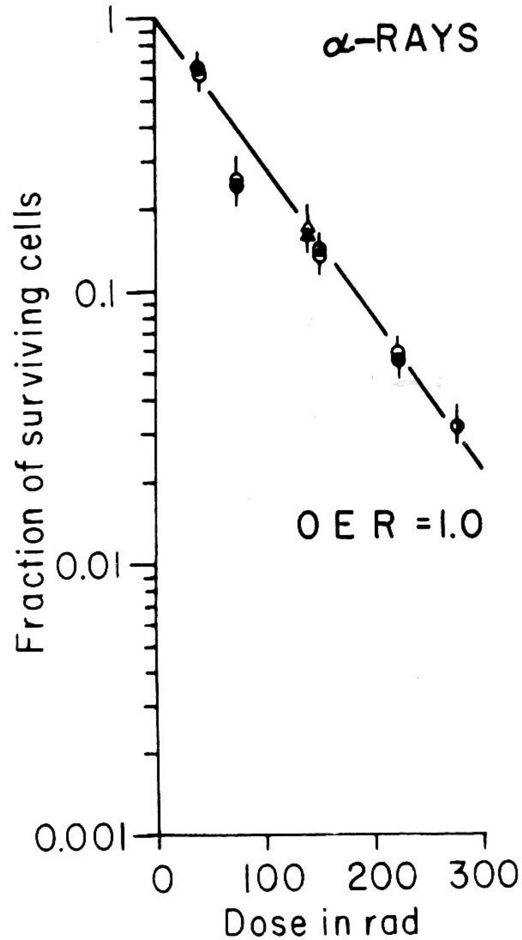
LETにピークがある理由ー１つの仮説



LETが低いと電離が疎らでDNA二重鎖切断が起こりにくい
しかし、高すぎると、余分な電離が多くなる(Overkilling説)

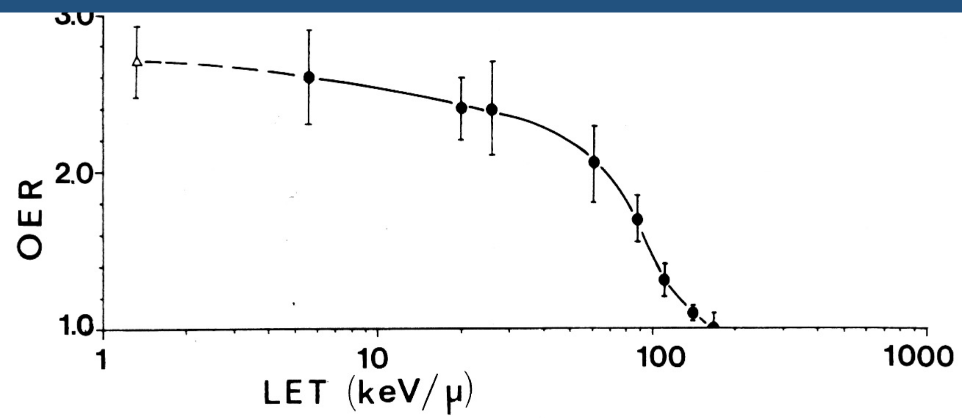
OER for high LET radiations

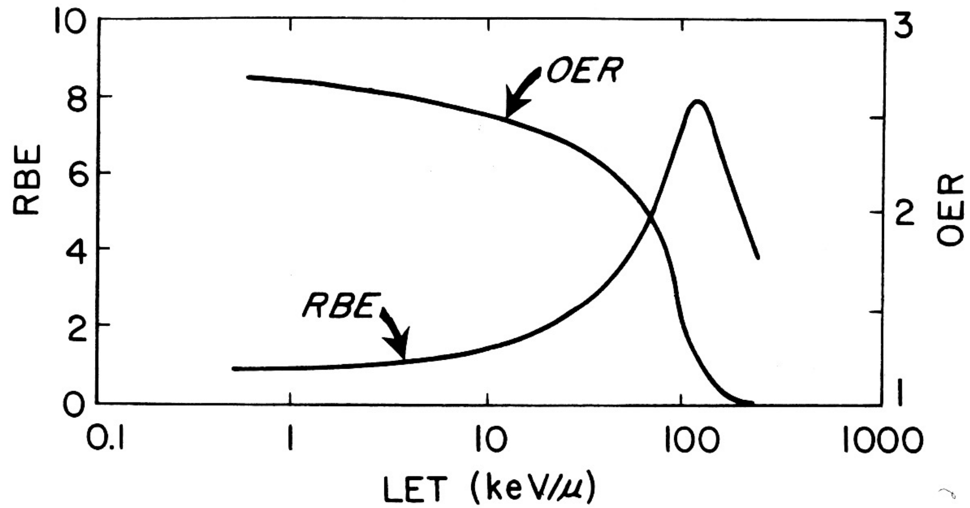




Cf. for X-ray OER=2.5

Interrelationship among LET, RBE and OER

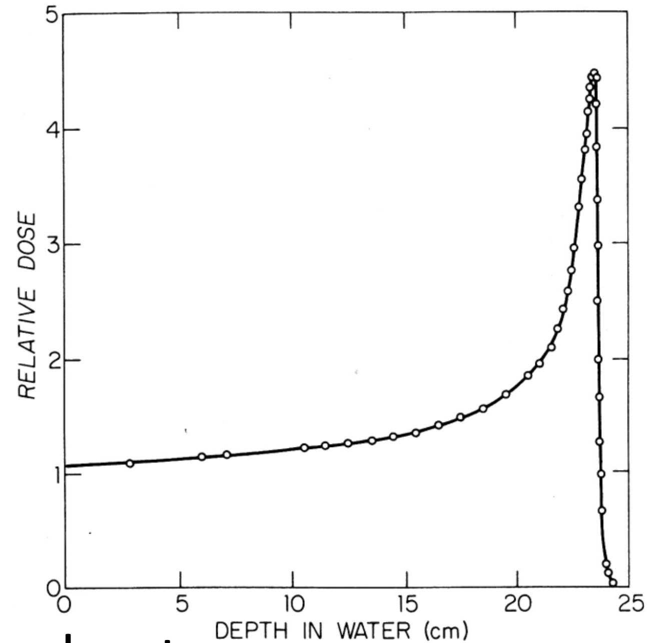




OER becomes smaller at high LET region

4. Heavy Ion Therapy

Bragg's peak of a charged particle



Charged particle decelerates

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Increased electrostatic interaction (energy deposit)

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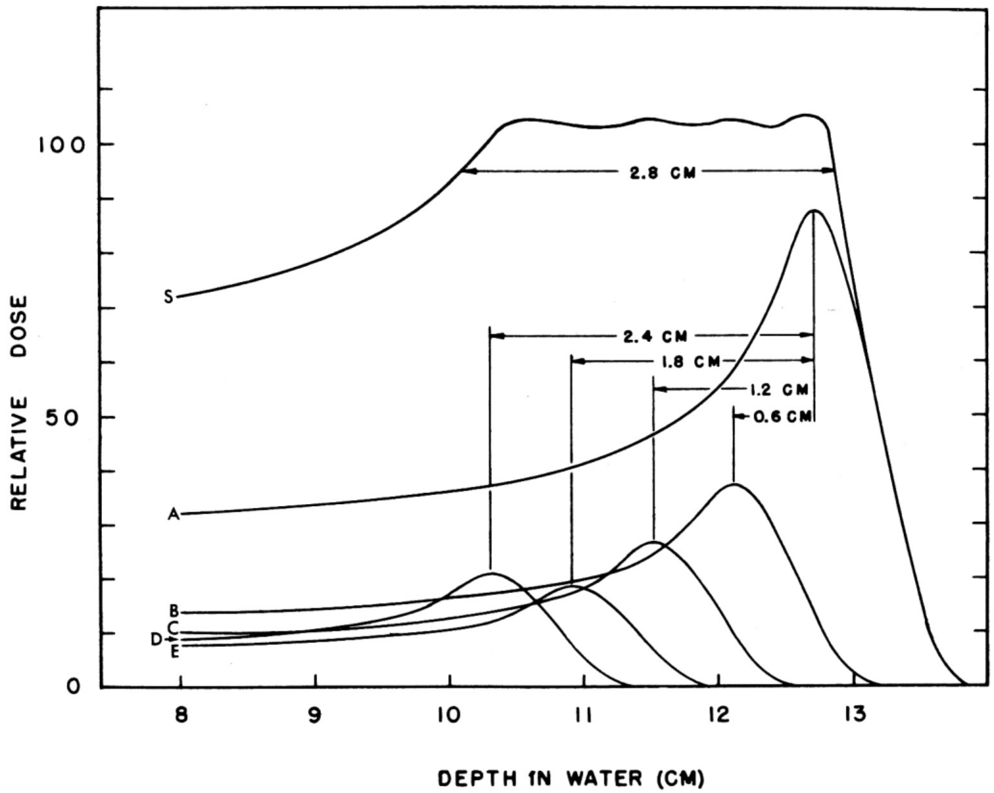
More deceleration, more energy deposit

↓

Deposit large energy immediately stops in motion

Spread-out Bragg's peak



By mixing beam with different Bragg peak, broadened area of peak radiation dose can be obtained

Characteristics of high LET radiations

1- High biological effects
(High RBE, less repair)
2- Low OER: effective even against hypoxic cells
3- (Charged particles) Excellent dose distribution due to Bragg's peak

高LET放射線の特長

1)RBEが大きい
　修復が小さい
　→　大きな生物効果

2)OERが小さい　→　低酸素細胞にも有効

3)(荷電粒子では)線量分布が良い
　→　周辺正常組織の障害の軽減

5. Boron Neutron Capture Therapy; BNCT（ホウ素中性子捕捉療法）

Principle of BNCT (1)

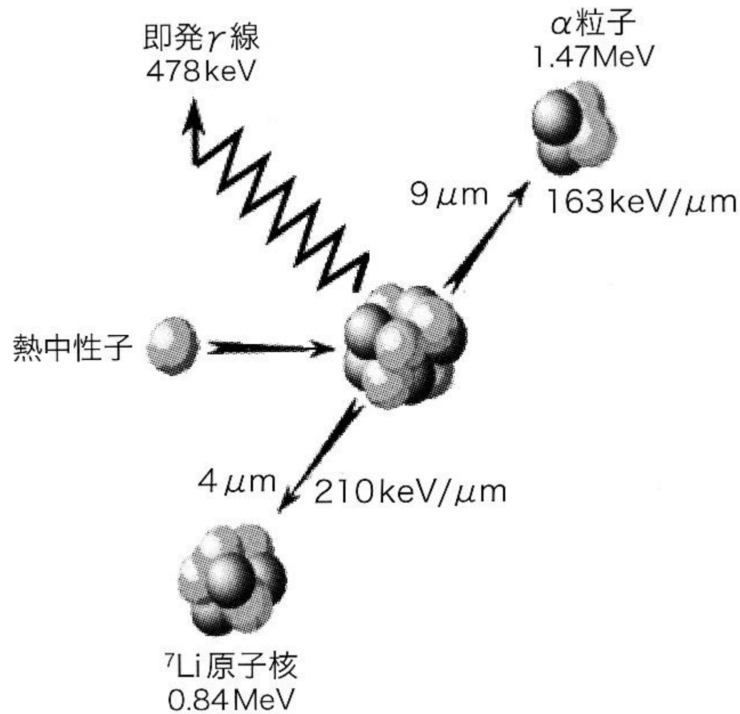


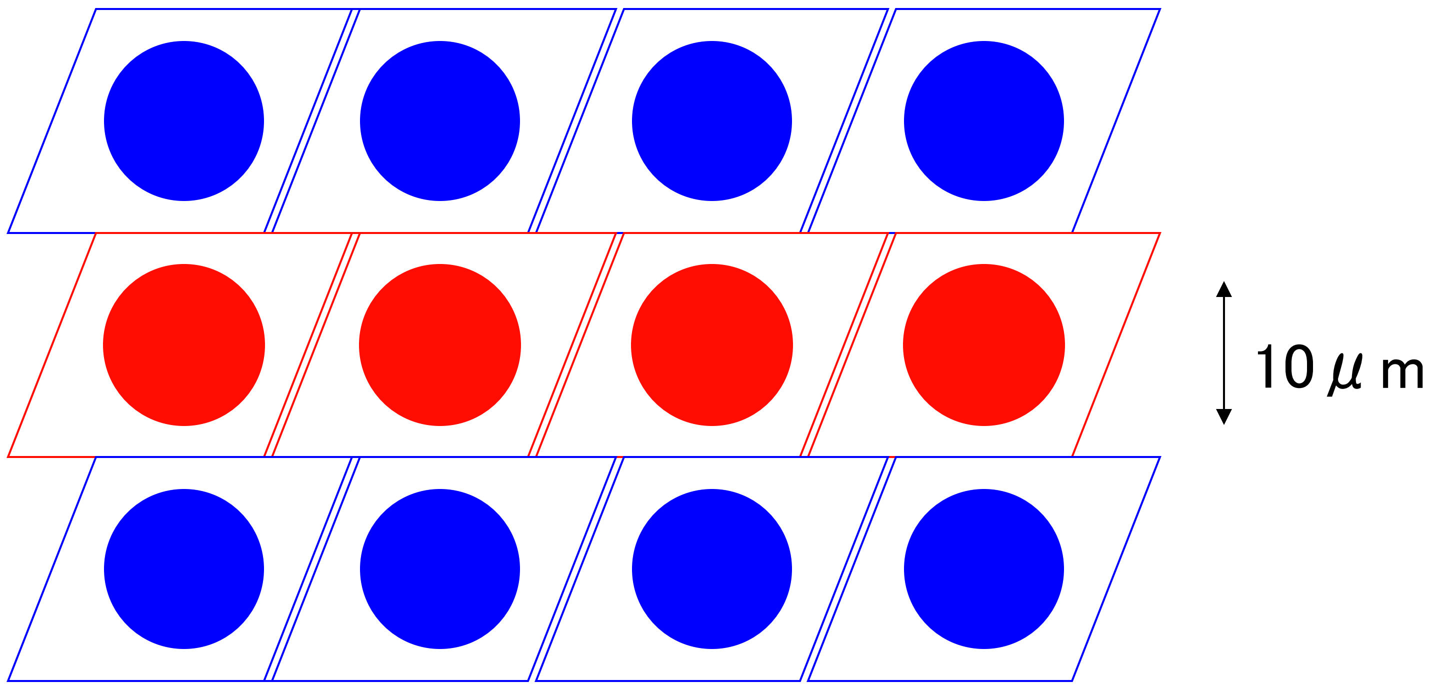
図 3.10.2　熱中性子の作用（^{10}B 原子核による捕獲反応）

① ^{10}B has a quite large thermal neutron capture cross section (3,837barn).

cf.) Largest among component atoms of body ^{13}N: 1.81barn

② Produce α particle and ^{7}Li recoiled nucleus, both of which have short paths.

Principle of BNCT (2)

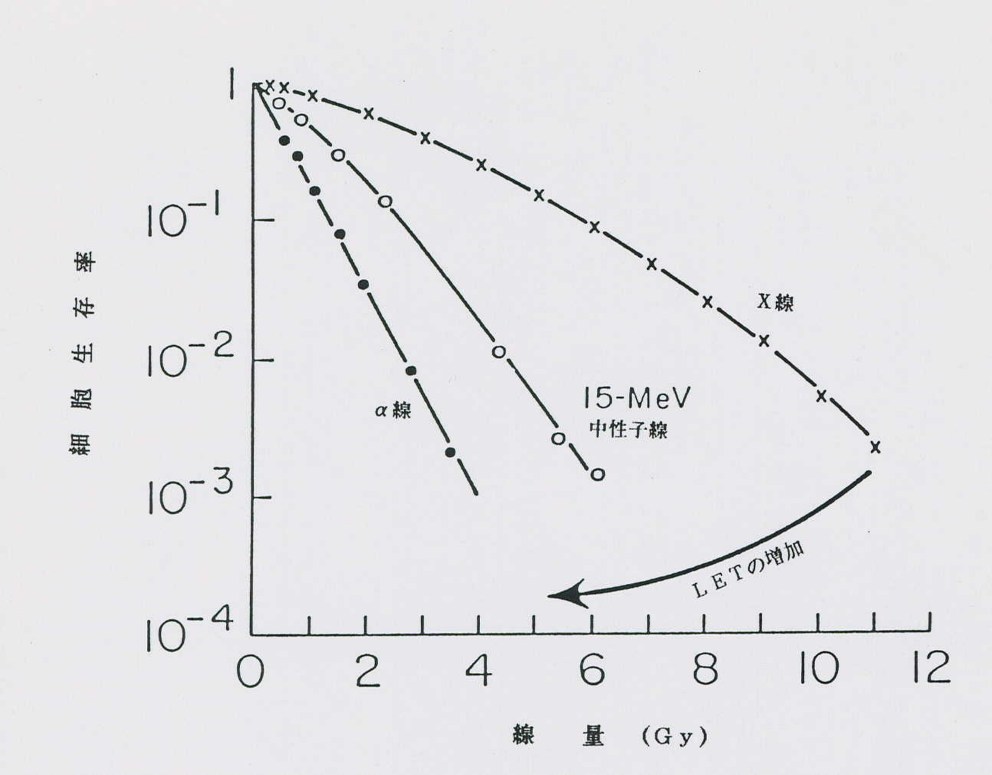


The paths for α and ^{7}Li are less than diameter of cell
→Only ^{10}B-incorporated cells are irradiated.

If ^{10}B compound is specifically uptaken by cancer,
The exposure of surrounding normal tissue will be minimal.

Principle of BNCT (3)

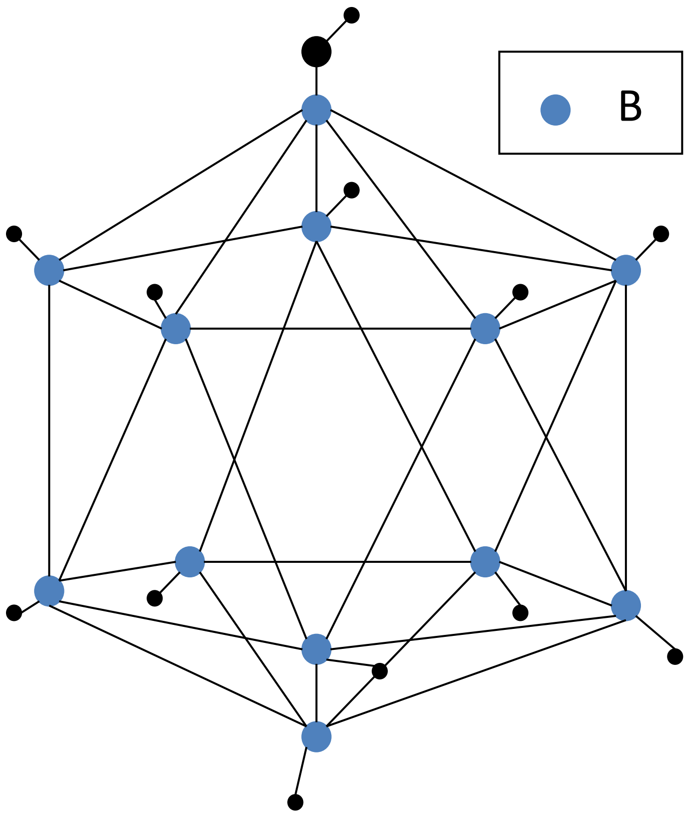
Biological effects of α-ray



1)High RBE, small repair → large biological effect

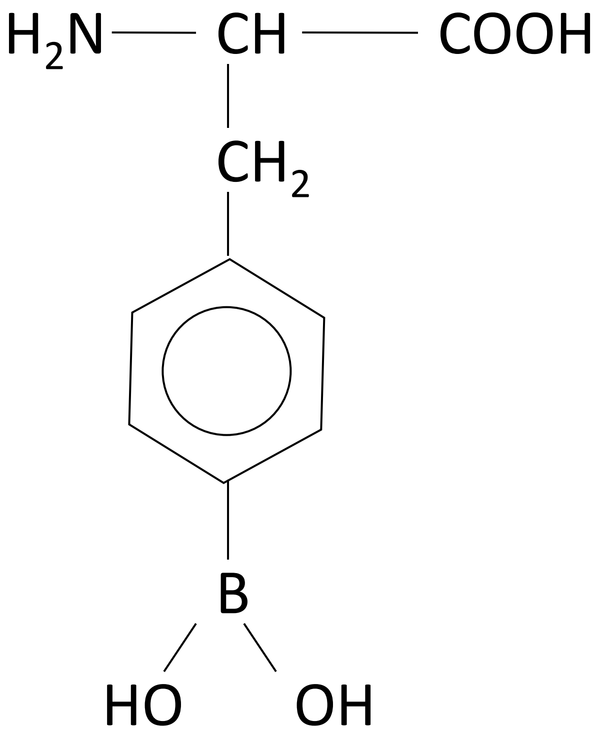
2)Small OER → Effective for hypoxic cell

Examples of BNCT drug



BSH(borocaptate)

Water soluble
Preferential accumulation to Brain tumor with broken blood-brain barrier



BPA(p-borono phenyl alanine)

Effectively incorporated into cancer cells, in which highly active protein synthesis is going on