Principle of oncology

เรียบเรียงโดย พญ.พิรญาณ์ ไทยเจียม
อาจารย์ที่ปรึกษา อ.พญ.วายูน วจะโนภาส

Oncology

Multidisciplinary team

- Surgeons
- Medical oncologists
- Radiation oncologists
- Reconstructive surgeons
- Pathologists
- Radiologists
- Primary care physicians

Definitions

- Primary (or definitive) therapy : en bloc resection of tumor with adequate margins of normal tissues and in some cases regional lymph nodes.

Estimated new cases*

			Males	Females			
Prostate	238,590	28%			Breast	232,340	29%
Lung & bronchus	118,080	14%			Lung & bronchus	110,110	14%
Colorectum	73,680	9%			Colorectum	69,140	9%
Urinary bladder	54,610	6%			Uterine corpus	49,560	6%
Melanoma of the skin	45,060	5%			Thyroid	45,310	6%
Kidney & renal pelvis	40,430	5%			Non-Hodgkin lymphoma	32,140	4%
Non-Hodgkin lymphoma	37,600	4%			Melanoma of the skin	31,630	4%
Oral cavity & pharynx	29,620	3%			Kidney & renal pelvis	24,720	3%
Leukemia	27,880	3%			Pancreas	22,480	3%
Pancreas	22,740	3%			Ovary	22,240	3%
All Sites	**854,790**	**100%**			**All Sites**	**805,500**	**100%**

Estimated deaths

			Males	Females			
Lung & bronchus	87,260	28%			Lung & bronchus	72,220	26%
Prostate	29,720	10%			Breast	39,620	14%
Colorectum	26,300	9%			Colorectum	24,530	9%
Pancreas	19,480	6%			Pancreas	18,980	7%
Liver & intrahepatic bile duct	14,890	5%			Ovary	14,030	5%
Leukemia	13,660	4%			Leukemia	10,060	4%
Esophagus	12,220	4%			Non-Hodgkin lymphoma	8,430	3%
Urinary bladder	10,820	4%			Uterine corpus	8,190	3%
Non-Hodgkin's lymphoma	10,590	3%			Liver & intrahepatic bile duct	6,780	2%
Kidney & renal pelvis	8,780	3%			Brain & other nervous system	6,150	2%
All Sites	**306,920**	**100%**			**All Sites**	**271,430**	**100%**

Figure 10-1. Ten leading cancer types with the estimated new cancer cases and deaths by sex in the United States, 2013. *Excludes basal and squamous cell skin cancers and in situ carcinomas except those of the urinary bladder. Estimates are rounded to the nearest 10 (*Modified with permission from John Wiley and Sons: Siegel R et al.* Cancer statistics, 2013. *CA: a cancer journal for clinicians. 2013;63:11. © 2013 American Cancer Society, Inc.*)

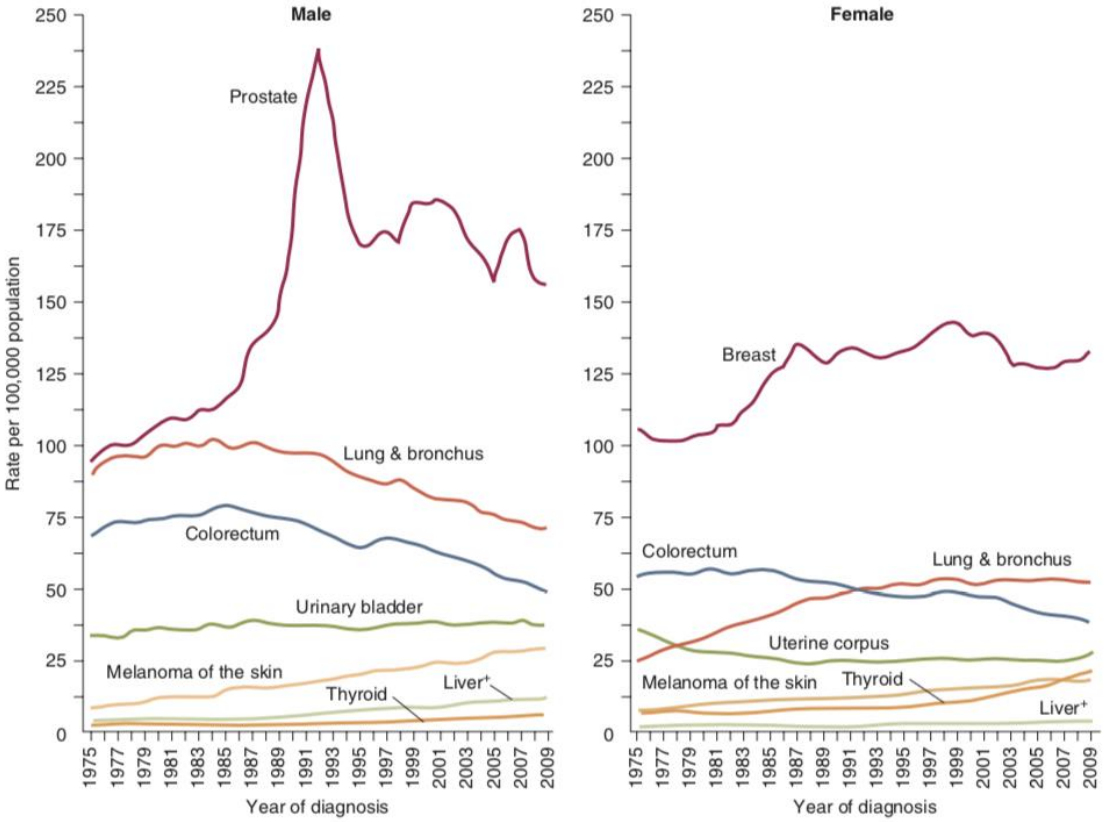


Figure 10-2. Trends in cancer incidence rates for selected cancer by sex among males and females for selected cancer types, United States, 1975 to 2009. Rates are age adjusted to the 2000 U.S. standard population. (*Modified with permission from John Wiley and Sons: Siegel R et al.* Cancer statistics, 2013. *CA: a cancer journal for clinicians. 2013;63:11. © 2013 American Cancer Society, Inc.*)[1]
+Liver includes intrahepatic bile duct

ตาราง 3 จำนวนผู้ป่วยมะเร็งรายใหม่ 15 อันดับแรก จำแนกตามเพศ พ.ศ. 2558
Table 3 The leading site of new cancer patient by sex: 2015

Ordinal	Site	Male		Female		Total	
		No.	%	No.	%	No.	%
1.	Breast	1	0.03	848	24.66	849	24.69
2.	Colon & Rectum	231	6.72	175	5.09	406	11.81
3.	Liver & Intrahepatic bile ducts	287	8.35	91	2.65	378	10.99
4.	Trachea, Bronchus & Lung	225	6.54	135	3.93	360	10.47
5.	Cervix uteri	0	0	283	8.23	283	8.23
6.	Lip & Oral cavity	73	2.12	40	1.16	113	3.29
7.	Corpus uteri	0	0	100	2.91	100	2.91
8.	Ovary	0	0	88	2.56	88	2.56
9.	Esophagus	82	2.38	5	0.15	87	2.53
10.	Stomach	42	1.22	34	0.99	76	2.21
11.	Prostate gland	73	2.12	0	0	73	2.12
12.	Non-Hodgkins lymphoma	39	1.13	25	0.73	64	1.86
13.	Nasopharynx	40	1.16	11	0.32	51	1.48
14.	Skin	26	0.76	21	0.61	47	1.37
15.	Larynx	41	1.19	2	0.06	43	1.25

- Adjuvant therapy : refers to radiation therapy and systemic therapies, including chemotherapy, immunotherapy, hormonal therapy, and increasingly, biologic therapy.

Goals of treatment

- Primary goal of surgical and radiation therapy : local and regional control
- Primary goal of systemic therapies : systemic control by treating distant foci of subclinical disease to prevent recurrence.

Acquired capabilities of cancer

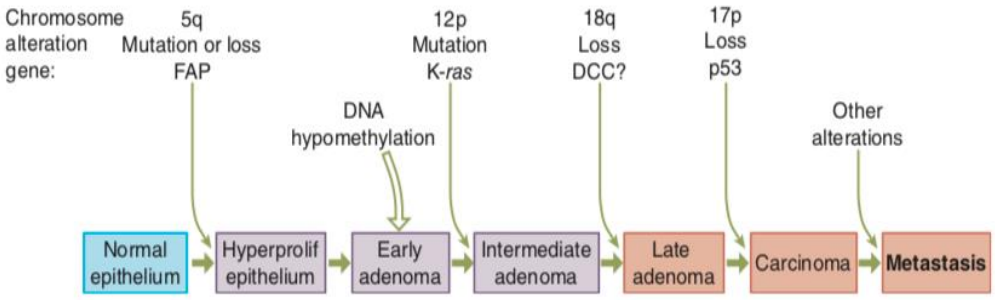


Figure 10-5. A genetic model for colorectal tumorigenesis. Tumorigenesis proceeds through a series of genetic alterations involving oncogenes and tumor-suppressor genes. In general, the three stages of adenomas represent tumors of increasing size, dysplasia, and villous content. Individuals with familial adenomatous polyposis (FAP) inherit a mutation on chromosome arm 5q. In tumors arising in individuals without polyposis, the same region may be lost or mutated at a relatively early stage of tumorigenesis. A *ras* gene mutation (usually K-*ras*) occurs in one cell of a pre-existing small adenoma which, through clonal expansion, produces a larger and more dysplastic tumor. The chromosome arms most frequently deleted include 5q, 17p, and 18q. Allelic deletions of chromosome arms 17p and 18q usually occur at a later stage of tumorigenesis than do deletions of chromosome arm 5q or *ras* gene mutations. The order of these changes varies, however, and accumulation of these changes, rather than their order of appearance, seems most important. Tumors continue to progress once carcinomas have formed, and the accumulated chromosomal alterations correlate with the ability of the carcinomas to metastasize and cause death. DCC = deleted in colorectal cancer gene. (*Modified with permission from Fearon et al. Copyright Elsevier.*)[9]

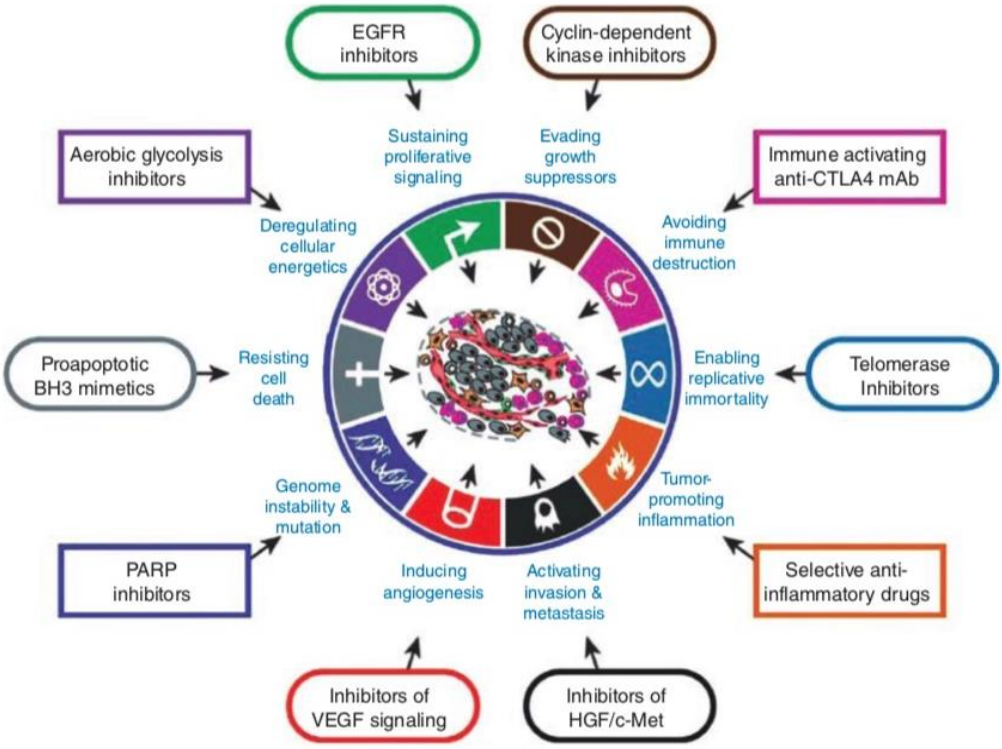


Figure 10-4. Hallmarks of cancer and their therapeutic implications. Drugs that interfere with each of the acquired capabilities necessary for tumor growth and progression are in clinical trials and in some cases approved for clinical use in treating forms of human cancer. The drugs listed are illustrative examples.(*Modified with permission from Hanahan et al. Copyright Elsevier.*)[7]

Metastatic process

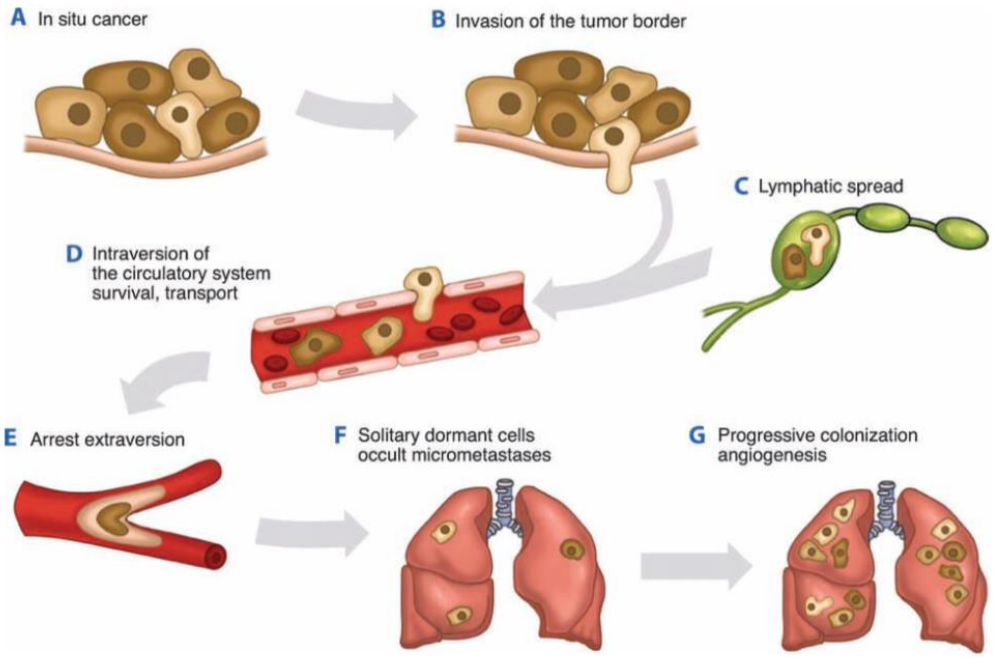
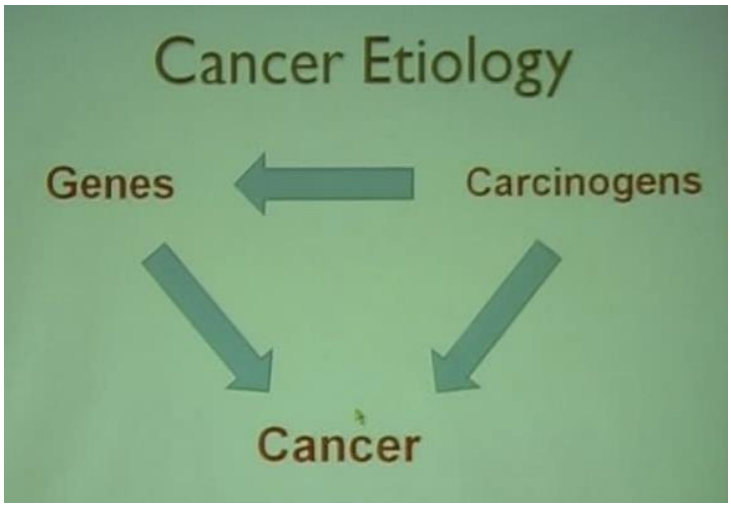


Figure 10-8. A schematic representation of the metastatic process. **A.** The metastatic process begins with an in situ cancer surrounded by an intact basement membrane. **B.** Invasion requires reversible changes in cell-cell and cell–extracellular matrix adherence, destruction of proteins in the matrix and stroma, and motility. **C.** Metastasizing cells can enter the circulation via the lymphatics. **D.** They can also directly enter the circulation. **E.** Intravascular survival of the tumor cells and extravasation of the circulatory system follow. **F.** Metastatic single cells can colonize sites and remain dormant for years as occult micrometastases. **G.** Subsequent progression and neovascularization leads to clinically detectable metastases and progressively growing, angiogenic metastases. (*Adapted by permission from Macmillan Publishers Ltd. Steeg PS. Metastasis suppressors alter the signal transduction of cancer cells.* Nat Rev Cancer. *2003;3:55. Copyright © 2003.*)[27]

Tumorigenesis

Cancer etiology



Genes

- Oncogenes
- Tumor suppressor genes

  Genes associated with hereditary cancer

Table 10-3

Selected genes associated with hereditary cancer

SYMBOL	NAME	TUMOR TYPES (GERMLINE MUTATIONS)	CANCER SYNDROME
ALK	anaplastic lymphoma kinase (Ki-1)	Neuroblastoma	Familial neuroblastoma
APC	adenomatous polyposis of the colon gene	Colorectal, pancreatic, desmoid, hepatoblastoma, glioma, other CNS	Adenomatous polyposis coli; Turcot syndrome
ATM	ataxia telangiectasia mutated	Leukemia, lymphoma, medulloblastoma, glioma	Ataxia-telangiectasia
BLM	Bloom Syndrome	Leukemia, lymphoma, skin squamous cell, other cancers	Bloom Syndrome
BMPR1A	bone morphogenetic protein receptor, type IA	Gastrointestinal polyps	Juvenile polyposis
BRCA1	familial breast/ovarian cancer gene 1	Breast, ovarian	Hereditary breast/ovarian cancer
BRCA2	familial breast/ovarian cancer gene 2	Breast, ovarian, pancreatic	Hereditary breast/ovarian cancer
BRIP1	BRCA1 interacting protein C-terminal helicase 1	AML, leukemia, breast	Fanconi anaemia J, breast cancer susceptiblity
BUB1B	BUB1 budding uninhibited by benzimidazoles 1 homolog beta (yeast)	Rhabdomyosarcoma	Mosaic variegated aneuploidy
CDH1	cadherin 1, type 1, E-cadherin (epithelial) (ECAD)	Gastric, lobular cancer	Familial gastric carcinoma
CDK4	cyclin-dependent kinase 4	Melanoma	Familial malignant melanoma
CDKN2A	cyclin-dependent kinase inhibitor 2A (p16(INK4a)) gene	Melanoma, pancreatic	Familial malignant melanoma
CDKN2a(p14)	cyclin-dependent kinase inhibitor 2A– p14ARF protein	Melanoma, pancreatic	Familial malignant melanoma
CHEK2	CHK2 checkpoint homolog (*S. pombe*)	Breast	Familial breast cancer
CYLD	familial cylindromatosis gene	Cylindroma	Familial cylindromatosis
DDB2	damage-specific DNA binding protein 2	Skin basal cell, skin squamous cell, melanoma	Xeroderma pigmentosum (E)
DICER1	dicer 1, ribonuclease type III	Pleuropulmonary blastoma	Familial Pleuropulmonary Blastoma
EGFR	epidermal growth factor receptor (erythroblastic leukemia viral (v-erb-b) oncogene homolog, avian)	NSCLC	Familial lung cancer
ERCC2, 3, 4, 5	excision repair cross-complementing rodent repair deficiency, complementation group	Skin basal cell, skin squamous cell, melanoma	Xeroderma pigmentosum (D, B, F, G))
EXT1	multiple exostoses type 1 gene	exostoses, osteosarcoma	exostoses, osteosarcoma
FANCA, C, D2, E, F, G	Fanconi anemia, complementation group	AML, leukemia	Fanconi anaemia A, C, D2, E, F, G
FH	fumarate hydratase	leiomyomatosis, renal	Hereditary leiomyomatosis and renal cell cancer
GPC3	glypican 3	Wilms' tumor	Simpson-Golabi-Behmel syndrome
HRAS	v-Ha-ras Harvey rat sarcoma viral oncogene homolog	v-Ha-ras Harvey rat sarcoma viral oncogene homolog	Costello syndrome
HRPT2	Hyperparathyroidism 2 (parafibromin)	parathyroid adenoma, mulitiple ossifying jaw fibroma	Hyperparathyroidism-jaw tumor syndrome
KIT	v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog	GIST, epithelioma	Familial gastrointestinal stromal tumor

Table 10-3

Selected genes associated with hereditary cancer (continued)

SYMBOL	NAME	TUMOR TYPES (GERMLINE MUTATIONS)	CANCER SYNDROME
MADH4	Homolog of *Drosophila* Mothers Against Decapentaplegic 4 gene	Gastrointestinal polyps	Juvenile polyposis
MEN1	multiple endocrine neoplasia type 1 gene	Parathyroid adenoma, pituitary adenoma, pancreatic islet cell, carcinoid	Parathyroid adenoma, pituitary adenoma, pancreatic islet cell, carcinoid
MLH1	*E. coli* MutL homolog gene	Colorectal, endometrial, ovarian, CNS	Hereditary nonpolyposis colorectal cancer, Turcot syndrome
MPL	myeloproliferative leukemia virus oncogene, thrombopoietin receptor	MPD	Familial essential thrombocythemia
MSH2	mutS homolog 2 (*E. coli*)	colorectal, endometrial, ovarian	Hereditary non-polyposis colorectal cancer
MSH6	mutS homolog 6 (*E. coli*)	colorectal, endometrial, ovarian	Hereditary non-polyposis colorectal cancer
MUTYH	mutY homolog (*E. coli*)	Colorectal	Adenomatous polyposis coli
NBS1	Nijmegen breakage syndrome 1 (nibrin)	NHL, glioma, medulloblastoma, rhabdomyosarcoma	Nijmegen breakage syndrome
NF1	neurofibromatosis type 1 gene	Neurofibroma, glioma	Neurofibromatosis type 1
NF2	neurofibromatosis type 2 gene	Meningioma, acoustic neuroma	Neurofibromatosis type 2
PALB2	partner and localizer of BRCA2	Wilms tumor, medulloblastoma, AML, breast	Fanconi anaemia N, breast cancer susceptibility
PHOX2B	paired-like homeobox 2b	Neuroblastoma	Familial neuroblastoma
PMS1	PMS1 postmeiotic segregation increased 1 (*S. cerevisiae*)	Colorectal, endometrial, ovarian	Hereditary non-polyposis colorectal cancer
PMS2	PMS2 postmeiotic segregation increased 2 (*S. cerevisiae*)	Colorectal, endometrial, ovarian, medulloblastoma, glioma	Hereditary nonpolyposis colorectal cancer, Turcot syndrome
PRKAR1A	protein kinase, cAMP-dependent, regulatory, type I, alpha (tissue specific extinguisher 1)	Myxoma, endocrine, papillary thyroid	Carney complex
PTCH	Homolog of *Drosophila* Patched gene	Skin basal cell, medulloblastoma	Nevoid Basal Cell Carcinoma Syndrome
PTEN	phosphatase and tensin homolog gene	Hamartoma, glioma, prostate, endometrial	Cowden Syndrome, Bannayan-Riley-Ruvalcaba syndrome
RB1	retinoblastoma gene	Retinoblastoma, sarcoma, breast, small cell lung	Familial retinoblastoma
RECQL4	RecQ protein-like 4	Osteosarcoma, skin basal and squamous cell	Rothmund-Thompson Syndrome
RET	ret proto-oncogene	Medullary thyroid, papillary thyroid, pheochromocytoma	Multiple endocrine neoplasia 2A/2B
SBDS	Shwachman-Bodian-Diamond syndrome protein	AML, MDS	Schwachman-Diamond syndrome
SDH5	chromosome 11 open reading frame 79	Paraganglioma	Familial paraganglioma
SHD, B, D	succinate dehydrogenase complex	Paraganglioma, pheochromocytoma	Familial paraganglioma

Table 10-3

Selected genes associated with hereditary cancer (continued)

SYMBOL	NAME	TUMOR TYPES (GERMLINE MUTATIONS)	CANCER SYNDROME
SMARCB1	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily b, member 1	Malignant rhabdoid	Rhabdoid predisposition syndrome
STK11	serine/threonine kinase 11 gene (LKB1)	Jejunal hamartoma, ovarian, testicular, pancreatic	Peutz-Jeghers syndrome
SUFU	suppressor of fused homolog (*Drosophila*)	Medulloblastoma	Medulloblastoma predisposition
TCF1	transcription factor 1, hepatic (HNF1)	Hepatic adenoma, hepatocellular carcinoma	Familial Hepatic Adenoma
TP53	tumor protein p53	Breast, sarcoma, adrenocortical carcinoma, glioma, multiple other tumor types	Li-Fraumeni syndrome
TSC1	tuberous sclerosis 1 gene	Hamartoma, renal cell	Tuberous sclerosis 1
TSC2	tuberous sclerosis 2 gene	Hamartoma, renal cell	Tuberous sclerosis 2
TSHR	thyroid stimulating hormone receptor	Thyroid adenoma	
VHL	von Hippel-Lindau syndrome gene	Renal, hemangioma, pheochromocytoma	von Hippel-Lindau syndrome
WRN	Werner syndrome (RECQL2)	Osteosarcoma, meningioma, others	Werner Syndrome
WT1	Wilms' tumor 1 gene	Wilms'	Denys-Drash syndrome, Frasier syndrome, Familial Wilms tumor
XPA, C	xeroderma pigmentosum, complementation group	Skin basal cell, skin squamous cell, melanoma	Xeroderma pigmentosum (A C)

A, amplification; **AEL**, acute eosinophilic leukemia; **AL**, acute leukemia; **ALCL**, anaplastic large-cell lymphoma; **ALL**, acute lymphocytic leukemia; **AML**, acute myelogenous leukemia; **AML***, acute myelogenous leukemia (primarily treatment associated); **APL**, acute promyelocytic leukemia; **B-ALL**, B-cell acute lymphocytic leukaemia; **B-CLL**, B-cell Lymphocytic leukemia; **B-NHL**, B-cell Non-Hodgkin Lymphoma; **CLL**, chronic lymphatic leukemia; **CML**, chronic myeloid leukemia; **CMML**, chronic myelomonocytic leukemia; **CNS**, central nervous system; **D**, large deletion; **DFSP**, dermatofibrosarcoma protuberans; **DLBL**, diffuse large B-cell lymphoma; **DLCL**, diffuse large-cell lymphoma; **Dom**, dominant; **E**, epithelial; **F**, frameshift; **GIST**, gastrointestinal stromal tumour; **JMML**, juvenile myelomonocytic leukemia; **L**, leukaemia/lymphoma; **M**, mesenchymal; **MALT**, mucosa-associated lymphoid tissue lymphoma; **MDS**, myelodysplastic syndrome; **Mis**, Missense; **MLCLS**, mediastinal large cell lymphoma with sclerosis; **MM**, multiple myeloma; **MPD**, Myeloproliferative disorder; **N**, nonsense; **NHL**, non-Hodgkin lymphoma; **NK/T**, natural killer T cell; **NSCLC**, non small cell lung cancer; **O**, other; **PMBL**, primary mediastinal B-cell lymphoma; **pre-B All**, pre-B-cell acute lymphoblastic leukaemia; **Rec**, recessive; **S**, splice site; **T**, translocation; **T-ALL**, T-cell acute lymphoblastic leukemia; **T-CLL**, T-cell chronic lymphocytic leukaemia; **TGCT**, testicular germ cell tumour; **T-PLL**, T cell prolymphocytic leukemia

Source: *Adapted by permission from Macmillan Publishers Ltd. Futreal PA et al. A census of human cancer genes.* Nat Rev Cancer. *2004;4:177. Copyright © 2004.*

Criteria suggest of hereditary cancer

- Tumor development at much younger age than usual.
- Presence of bilateral disease.
- Presence of multiple primary malignancies.
- Presentation of a cancer in the less affected sex. (eg male with breast cancer)
- Clustering of the same cancer type in relatives.
- Cancer associated with other condition such as mental retardation.

Carcinogens

- Chemical carcinogens
- Physical carcinogens
- Viral carcinogens

Table 10-5

Group 1 chemical carcinogens and evidence for carcinogenicity in humans and for genotoxicity as the main mechanism

	TUMOR SITES OR TYPES WITH SUFFICIENT EVIDENCE IN HUMANS	EVIDENCE OF GENOTOXICITY AS THE MAIN MECHANISM
4-Aminobiphenyl	Urinary bladder	Strong
Benzidine	Urinary bladder	Strong
Dyes metabolized to benzidine	..	Strong*
4,4'-Methylenebis(2-chloroaniline)	..	Strong*
2-Napthylamine	Urinary bladder	Strong
Ortho-toluidine	Urinary bladder	Moderate
Auramine production	Urinary bladder	Weak/lack of data†
Magenta production	Urinary bladder	Weak/lack of data†
Benzo[α]pyrene	..	Strong*
Soot (chimney sweeping)	Skin, lung	Moderate
Coal gasification	Lung	Strong
Coal-tar distillation	Skin	Strong
Coke production	Lung	Strong
Coal-tar pitches (paving, roofing)	Lung	Strong
Aluminum production	Lung, urinary bladder	Weak/moderate†‡
Aflatoxins	Hepatocellular carcinoma	Strong
Benzene	ANLL	Strong
Bis(chloromethyl)ether/ chloromethyl methylether	Lung	Moderate/strong
1,3-Butadiene	Haematolymphatic organs	Strong
Dioxin (2,3,7,8-TCDD)	All cancers combined**	See text§
2,3,4,7,8-Pentachlorodibenzofuran	..	See text*§
3,3',4,4',5-Pentachlorobiphenyl (PCB-126)	..	See text*§
Ethylene oxide	..	Strong*
Formaldehyde	Nasopharynx Leukemia**	Strong Moderate
Sulfur mustard	Lung	Strong
Vinyl chloride	Hepatic angiosarcoma, hepatocellular carcinoma	Strong
Iron and steel founding	Lung	Weak/moderate
Isopropyl alcohol manufacture using strong acids	Nasal cavity	Weak/lack of data
Mineral oils	Skin	Weak/lack of data
Occupational exposure as a painter	Lung, urinary bladder, pleural mesothelioma	Strong‡
Rubber-manufacturing industry	Leukaemia, lymphoma**, urinary bladder, lung**, stomach**	Strong‡
Shale oils	Skin	Weak/lack of data
Strong inorganic acid mists	Larynx	Weak/lack of data

ANLL, acute non-lymphocytic leukaemia; **ALL**, acute lymphocytic leukaemia; **CLL**, chronic lymphocytic leukaemia; **MM**, multiple myeloma; **NHL**, non-Hodgkin lymphoma; **STS**, soft-tissue sarcoma.
*Agents classified in Group 1 on the basis of mechanistic information.
†Weak evidence in workers, but strong evidence for some chemicals in this industry.
‡Due to the diversity and complexity of these exposures, other mechanisms may also be relevant.
§Strong evidence for an aryl hydrocarbon receptor (AhR)-mediated mechanism.
¶Particularly myeloid leukemia.
‖After maternal exposure (before or during pregnancy, or both).
**New epidemiological findings.
Source: Adapted from Baan et al 2009. Copyright Elsevier.[86]

IARC group I chemical carcinogens

- Selected viral carcinogens

Table 10-6

Selected viral carcinogens[a]

VIRUS	PREDOMINANT TUMOR TYPE[b]
Epstein-Barr virus	Burkitt's lymphoma
	Hodgkin's disease
	Immunosuppression-related lymphoma
	Sinonasal angiocentric T-cell lymphoma
	Nasopharyngeal carcinoma
Hepatitis B virus	Hepatocellular carcinoma
Hepatitis C virus	Hepatocellular carcinoma
HIV type 1	Kaposi's sarcoma
	Non-Hodgkin's lymphoma
Human papillomavirus 16 and 18	Cervical cancer
	Anal cancer
Human T-cell lymphotropic viruses	Adult T-cell leukemia/lymphoma

[a]Data based on information in the International Agency for Research on Cancer monographs.[85]

[b]Only tumor types for which causal relationships are established are listed. Other cancer types may be linked to the agents with a lower frequency or with insufficient data to prove causality.

Cancer screening

Table 10-9

American Cancer Society recommendations for early detection of cancer in average-risk, asymptomatic individuals

CANCER SITE	POPULATION	TEST OR PROCEDURE	FREQUENCY
Breast	Women, aged ≥20y	BSE	It is acceptable for women to choose not to do BSE or to do BSE regularly (monthly) or irregularly. Beginning in their early 20s, women should be told about the benefits and limitations of BSE. Whether a woman ever performs BSE, the importance of prompt reporting of any new breast symptoms to a health professional should be emphasized. Women who choose to do BSE should receive instruction and have their technique reviewed on the occasion of a periodic health examination.
		CBE	For women in their 20s and 30s, it is recommended that CBE be part of a periodic health examination, preferably at least every 3 y. Asymptomatic women aged ≥40 y should continue to receive a CBE as part of a periodic health examination, preferably annually.
		Mammography	Begin annual mammography at age 40 y.[a]
Cervix	Woman, aged 21–65 y	Pap test and HPV DNA test	Cervical cancer screening should begin at age 21 y. For women aged 21–29 y, screening should be done every 3 y with conventional or liquid-based Pap tests. For women aged 30–65 y, screening should be done every 5 y with both the HPV test and the Pap test (preferred), or every 3 y with the Pap test alone (acceptable). Women aged >65 y who have had ≥3 consecutive negative Pap tests or ≥2 consecutive negative HPV and Pap tests within the last 10 y, with the most recent test occurring within the last 5 y, and women who have had a total hysterectomy should stop cervical cancer screening. Women at any age should not be screened annually by any screening method.
Colorectal	Men and women aged ≥50 y	FOBT with at least 50% test sensitivity for cancer, or FIT with at least 50% test sensitivity for cancer, or	Annual, starting at age 50 y. Testing at home with adherence to manufacturer's recommendation for collection techniques and number of samples is recommended. FOBT with the single stool sample collected on the clinician's fingertip during a DRE in the healthcare setting is not recommended. Guaiac-based toilet bowl FOBT tests also are not recommended. In comparison with guaiac-based tests for the detection of occult blood, immunochemical tests are more patient-friendly, and are likely to be equal or better insensitivity and specificity. There is no justification for repeating FOBT in response to an initial positive finding.
		Stool DNA test[b], or	Interval uncertain, starting at age 50 y.
		FSIG, or	Every 5 y, starting at age 50 y. FSIG can be performed alone, or consideration can be given to combining FSIG performed every 5 y with a highly sensitive guaiac-based FOBT or FIT performed annually.
		DCBE, or	Every 5 y, starting at age 50 y.
		Colonoscopy	Every 10 y, starting at age 50 y.
		CT colonography	Every 5 yr, starting at age 50 y.
Endometrial	Women, at menopause		At the time of menopause, women at average risk should be informed about the risks and symptoms of endometrial cancer and strongly encouraged to report any unexpected bleeding or spotting to their physicians.

Table 10-9

American Cancer Society recommendations for early detection of cancer in average-risk, asymptomatic individuals (continued)

CANCER SITE	POPULATION	TEST OR PROCEDURE	FREQUENCY
Lung	Current or former smokers aged 50–74 in good health with at least a 30 pack-year history	LDCT	Clinicians with access to high-volume, high-quality lung cancer screening and treatment centers should initiate a discussion about lung cancer screening with apparently healthy patients aged 55–74 y who have at least a 30 pack-y smoking history, and who currently smoke or have quit within the past 15 y. A process of informed and shared decision-making with a clinician related to the potential benefits, limitations, and harms associated with screening for lung cancer with LDCT should occur before any decision is made to initiate lung cancer screening. Smoking cessation counseling remains a high priority for clinical attention in discussions with current smokers, who should be informed of their continuing risk of lung cancer. Screening should not be viewed as an alternative to smoking cessation.
Prostate	Men, aged ≥50 y	DRE and PSA	Men who have at least a 10-y life expectancy should have an opportunity to make an informed decision with their health care provider about whether to be screened for prostate cancer, after receiving information about the potential benefits, risks, and uncertainties associated with prostate cancer screening. Prostate cancer screening should not occur without an informed decision-making process.
Cancer-related checkup	Men and women aged ≥20 y		On the occasion of a periodic health examination, the cancer-related checkup should include examination for cancers of the thyroid, testicles, ovaries, lymph nodes, oral cavity, and skin, as well as health counseling about tobacco, sun exposure, diet and nutrition, risk factors, sexual practices, and environmental and occupational exposures.

ACS, American Cancer Society; **BSE**, breast self-examination; **CBE**, clinical breast examination; **Pap**, Papanicolaou; **HPV**, human papillomavirus; **FOBT**, fecal occult blood test; **FIT**, fecal immunochemical test; **DRE**, digital rectal examination; **FSIG**, flexible sigmoidoscopy; **DCBE**, double-contrast barium enema; **CT**, computed tomography; **LDCT**, low-dose helical CT; **PSA**, prostate-specific antigen.

[a]Beginning at age 40 y, annual CBE should ideally be performed prior to mammography.

[b]The stool DNA test approved for colorectal cancer screening in 2008 is no longer commercially available. New stool DNA tests are presently undergoing evaluation and may become available at some future time.

Source: Modified with permission from John Wiley and Sons: Smith RA et al. Cancer screening in the United States, 2013: a review of current American Cancer Society guidelines, current issues in cancer screening, and new guidance on cervical cancer screening and lung cancer screening. CA: a cancer journal for clinicians. 2013;63:87. © 2013 American Cancer Society, Inc.

Cancer staging

American Joint Committee on Cancer (AJCC)

Union Internationale Contre Cancer (International Union Against Cancer, UICC)

3 components:

- Primary tumor (T)
- Nodal metastases (N)
- Distant metastases (M).

**Clinical staging (cTNM or TNM), Pathologic staging(pTNM), re-treatment (rTNM) or autopsy staging (aTNM).

** TNM staging manual >> pdf

- https://cancerstaging.org/references-tools/deskreferences/Documents/AJCC6thEdCancerStagingManualPart1.pdf (2003)
- https://cancerstaging.org/references-tools/deskreferences/Pages/AJCC-7th-Ed-Cancer-Staging-Manual.aspx (7th ed, 2010)
- https://cancerstaging.org/references-tools/deskreferences/Pages/default.aspx (8th ed, effective 2018)

Tumor markers

Marker	Cancer	Sensitivity	Specificity
PSA	Prostate	57-93%	55-68%
CEA	Colorectal Breast Recurrent disease	40-47% 45% 84%	90% 81% 100%
AFP	Hepatocellular	98%	65%
CA19-9	Pancreatic	78-90%	95%
CA27-29	Breast	62%	83%
CA15-3	Breast	57%	87%

Roles of surgery in cancer

- Prevention
- Diagnosis
- Treatment

Prevention of cancer

- Some underlying conditions
- Congenital of genetic traits (intensive screening)
- High incidence of subsequent cancer

- Familial adenomatous polyposis (FAP)
- 50% develop colon cancer by age of 40
- By age 70, virtually all develop colon cancer.
- Prophylactic proctocolectomy before age 20 to prevent CRC is advised for who carry APC gene

- UC (ulcerative colitis)
- 40% of UC die of colon cancer
- 3% of children with UC develop colon cancer by the age of 10, and 20% develop cancer during each ensuing decade.
- Colectomy is indicated for patients with UC if the chronicity of this disease is well established.
- Breast cancer
- Risk of cancer in some women is increased substantially over the normal risk (but does not approach 100%)
- Counseling the explains the benefits and risks of prophylactic mastectomy.
- Genetic tests for BRCA1 and BRCA2 mutations provide valuable information.

Diagnosis of cancer

- Acquisition of tissue for exact histologic diagnosis > biopsy

Biopsy

- Aspiration : cystic lesion eg. Thyroid
- Needle : core of tissue (solid tumor) eg breast mass **Needle tract tumor seeding**, not work in sarcoma > cannot interpret pathology result.
- Incisional : removal of small wedge tissue from a larger tumor mass.
- Excisional : excision of entire suspected tumor tissue with little or no margin of surrounding normal tissue eg lymph node.

Treatment of cancer

- Curative resection of primary cancer
- Cytoreductive surgery
- Metastatic disease
- Oncologic emergencies
- Palliation
- Reconstruction and rehabilitation

Curative resection of primary cancer

- Definitive surgical therapy with sufficient margins is sufficient local therapy
- Wide excision of primary melanomas of skin can be cured locally by surgery alone 90% of cases.
- The resection of colon cancers with 5-cm margin from the tumor results in anastomotic recurrences in fewer than 5% of cases.
- Surgery obtain histology confirmation of diagnosis > primary local therapy is achieved through nonsurgical modality eg radiation therapy
- CA nasopharynx
- Long bones Ewing's sarcoma

- Lymphatic mapping & sentinel lymph node biopsy
- The magnitude of surgical resection is modified when use of neoadjuvant treatment (Rhabdomyosarcoma)
- Surgery alone > 5 year survival rates 10-20%
- Neoadjuvant radiation therapy combined with chemotherapy : long-term cure rates are now 80%.

Cytoreductive surgery

- Extensive local spread of cancer precludes the removal of all gross disease by surgery
- Partial surgical resection of bulk disease in selected cancers improves the ability of other treatment modalities to control unresectable residual gross disease.
- Cytoreductive surgery is of benefit only when other effective treatments are available to control unresectable residual disease.

Metastatic disease

- Single site of metastatic disease that can be resected without major morbidity should undergo resection.
- Limited lung, liver or brain metastases can be cured by surgical resection.
- Appropriate for cancers that not respond well to systemic chemotherapy.
- Resection of colorectal hepatic metastases, in whom the liver is the only site metastasis can leas to long term cure in 25%.

Oncologic emergencies

- Exsanguinating hemorrhage eg carotid blow out
- Perforation
- Drainage of abscesses
- Impending destruction of vital organs
- Advanced cancer : nonsurgical intervention >> endoscopic therapy, intervention radiology.

Palliation

- Relief of pain : pain medications, nerve block, epidural block, celiac ganglion block:EUS guide, pain clinic.
- Relief of functional abnormalities (relieve mechanical problems eg intestinal obstruction)
- Improve the quality of life.
- Advances stage : non surgical intervention : stent

Reconstruction and rehabilitation

- Reconstruction and rehabilitation after definitive treatment
- Improve function and cosmetic appearance
- Free flaps using microvascular anastomotic techniques is having a profound impact on the ability to bring fresh tissue to resected or heavily irradiated areas.

- Loss function (especially of extremities) often can be restore by surgical approaches.
- Lysis of contractures or muscle transposition to restore muscular function damaged by previous surgery or radiation therapy.

Principle of radiation therapy

Outlines

- Basic radiation physics
- Basic radiobiology
- Basic clinical radiation oncology - clinical application in different diseases

Basic radiation physics**

- Type of radiation delivery

  Teletherapy :

  External beam radiation theory

  Radiation : gradual fall off

  Brachytherapy :

  (ระยะใกล้)

  1. Intracavitary (ใส่ช่อง) nasopharynxCA, cervicalCA,
  2. Interstitial (เข็มเจาะ) prostate, partial breast radiation (in future), lower lip,
  3. Mold (แปะวาง) hard palate CA

  Radiation : rapid fall off (dose drop แปรผกผัน 1/distance2)

  Not expose to radiation personnel

  IORT (intra-operative radiation therapy) :

  External beam radiation therapy (need specific room)

  May decrease side effect to intraabdominal organs

  Inconvenient

  Limited facility

  Not uniform dose delivery.

Type of radiation

- Photon
- Electron
- Others: proton, neutron

Photon (Megavoltage)	Electron
Deeper penetration	Less penetration
Deep tumor	Rapid fall off
Energy of radiation will determine the depth of radiation penetration	Superficial tumor (<5cm deep from skin)
Higher beam energy > deeper penetration	Neck nodes, skin lesions, less skin sparing effect
Higher energy > less skin doses (skin sparing effect)	

Radiation doses

- Absorb dose : Gy (Gray)

  1 GY = 100cGy
- Fractionation (external beam radiation therapy)

  Conventional fractionation : 1.8-2 Gy/F, 1 F/day

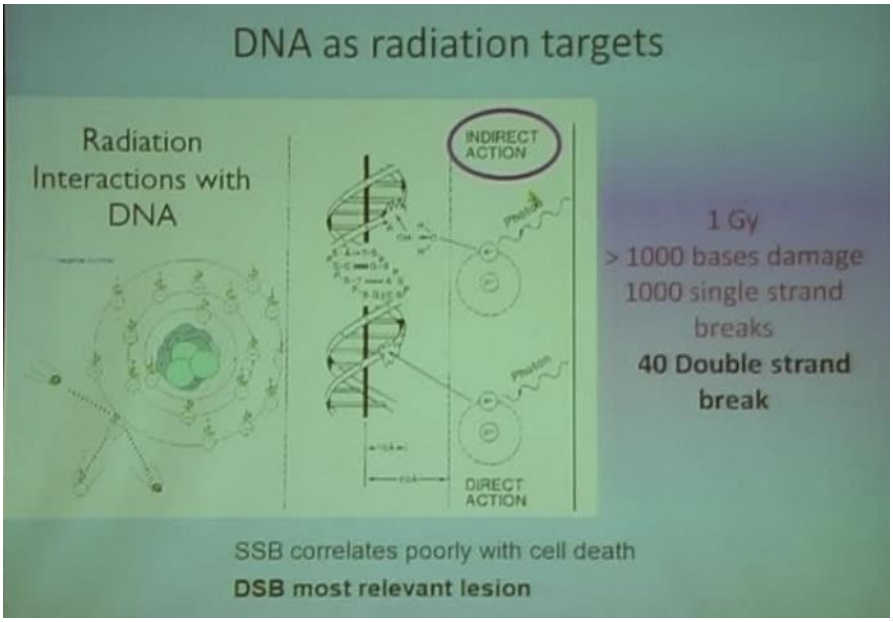
  Total dose : microscopic & post op : 50-60 Gy

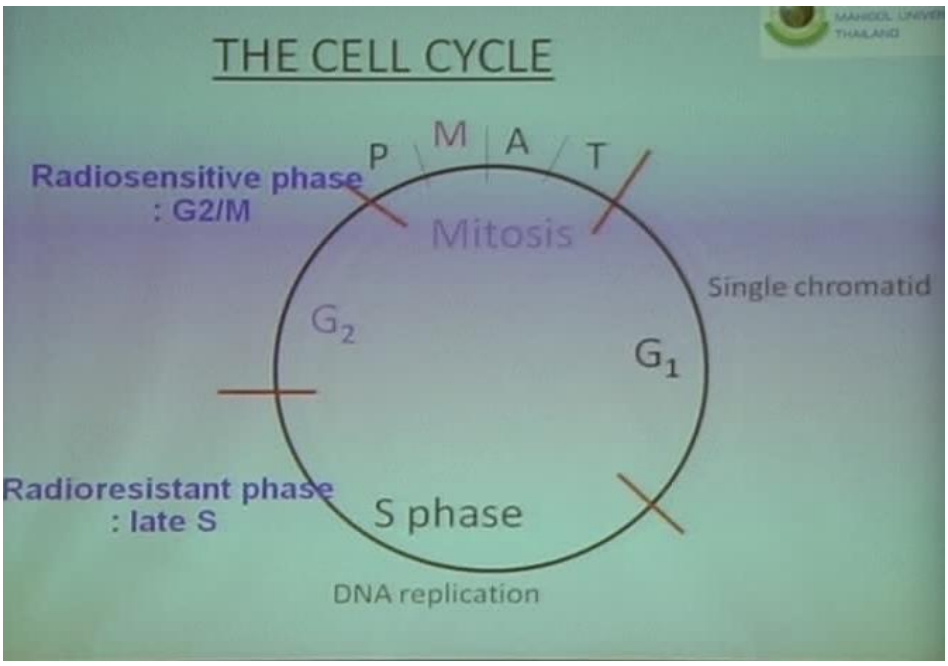
  Gross disease : 66-70 Gy

Basic radiobiology**

- Radiation actions : Targets of radiation
- Radiation responses
- Interactions with modifiers
- Chemotherapy
- Hyperthermia
- Biological agents

Radiation actions





4R's : Fractionated treatment

- Repair
- Redistribution (Reassortment)
- Reoxygenetion (hypoxic cells are radioresistant) ; re-sensitive radiotherapy
- Repopulation

Radiation responses

- Radiosensitive tumor (RS) : leukemia, lymphoma, germ cell tumor
- Relatively radiosensitive tumor (RRS) : Squamous cell carcinoma
- Relatively radio resistant tumor (RRR) : Adenocarcinoma
- Radioresistant tumor (RR) : sarcoma, melanoma

Radiation Response to normal tissues

- Cell types

1. Early responding tissues : effect during radiation. Treatment course : skin, epithelium, muscos, BM
2. Late responding tissues : long term side effect (>6 months after RT) : spinal cord, liver, kidney , bone, kidney

Concurrence chemoRT

- chemo as radiosensitizer
- Inhibit sublethal damage repair

Targeted therapy and radiation

- EGFR - cetuximam (C-225) (anti- EGFR) + RT

Basis for combining surgery and radiation therapy

- Plan : limitation of each modality when used alone
  Early stage : single modality
  Advance stage : combined modalities
- Salvage : when one modality failed

General radiotherapy principles

- High dose for gross disease : lower dose subclinical disease
- Minimize dose to adjacent normal tissues

Advantage of RT

- Preservation of tissue, function, and cosmetics
- Control of subclinical disease in the adjacent tissue with less morbidity
- Can simultaneously treat multiple primaries
- Better surgical salvage rate of XRT failures than XRT salvage rate of surgical failures
- Rare treatment mortality.

Disadvantage of RT

- Desirable acute side effects
- Potential late complications
- Induction of second malignancies (0.5%/year stop at 20-year)
- Protracted treatment course with external beam irradiation

Clinical radiation oncology**

Role of radiation therapy

- Curative treatment (depend on cell types, size, location)
  Definite tx : 66-70Gy, 2 Gy/F, 33-35 F
  Adjuvant tx 50-60 Gy, 2 Gy/F, 25-30 F
  Neoadjucant tx : 45-40 Gy, 2 Gy/F, 23-25 F
- Palliative treatment
  Local : primary tumor and/or neck nodes
  Distant : Bone, Brain
  40 Gy, 2 Gy/F, 20 F
  30 Gy, 3 Gy/F, 10 F
  20 Gy, 5 Gy/F, 4 F
  6-8 Gy, single fraction

Radiation treatment process

- Diagnosis
- Simulation
- Treatment planning
- Treatment delivery

Radiation positioning (set-up) and immobilization

- Individualized

IGRT

- Image Guided Radiation Therapy

Disease specific sites :

- CNS
- Role : postoperative (less definitive)
- Benign diseases : AVM, pituitary adenoma, meningioma, acoustic neuroma
- Malignant diseases : primary brain tumor , brain metastases (whole brain radiation therapy)
- Head & neck
- Role :
- Definitive : oropharynx (base of tongue, Tonsils, soft palate)
- Post-op : oral tongue, paranasal sinuses
- Breast
- Post-op tx
- Indications of post-op RT
    1. All patients with breast conservative surgery
    2. Post mastectomy RT in

       T3 (T>5cm), T4

       >/= 4 nodes

       Margins, +LVSI
- Definitive tx

  Inflammatory breast cancer

  Locally advanced disease
- Thoracic : lung cancer, esophageal cancer > IMRT
- Abdomen :
- Colorectal cancer (T4)

- Rectal cancer

  Pre-op RT

  - Sphincter preservation
  - Downstaging
  - Decrease side effect from post RT
  - Improve LR control compared to post-op RT

- Pediatrics :
- Non CNS > Wilm's tumor (Sx+CMT+RT), neuroblastoma
- CNS : medulloblastoma

Radiation side effects (within RT fields)

Acute side effects	Late side effects
Latency < 90 days	Latency > 3-6 months
During radiation tx	Typically 0.5-6 years after RT
Transient	Irreversible
Determined by accumulative radiation doses	Treatment for complications may relieve
	Radiation forgiveness
	Determined by total radiation doses and dose per fraction

Table 10-13

Local effects of radiation

ORGAN	ACUTE CHANGES	CHRONIC CHANGES
Skin	Erythema, wet or dry desquamation, epilation	Telangiectasia, subcutaneous fibrosis, ulceration
GI tract	Nausea, diarrhea, edema, ulceration, hepatitis	Stricture, ulceration, perforation, hematochezia
Kidney	—	Nephropathy, renal insufficiency
Bladder	Dysuria	Hematuria, ulceration, perforation
Gonads	Sterility	Atrophy, ovarian failure
Hematopoietic tissue	Lymphopenia, neutropenia, thrombocytopenia	Pancytopenia
Bone	Epiphyseal growth arrest	Necrosis
Lung	Pneumonitis	Pulmonary fibrosis
Heart	—	Pericarditis, vascular damage
Upper aerodigestive tract	Mucositis, xerostomia, anosmia	Xerostomia, dental caries
Eye	Conjunctivitis	Cataract, keratitis, optic nerve atrophy
Nervous system	Cerebral edema	Necrosis, myelitis

Systemic therapy

Scope :

- Overview of molecular genetics of cancer
- Principles of systemic therapy

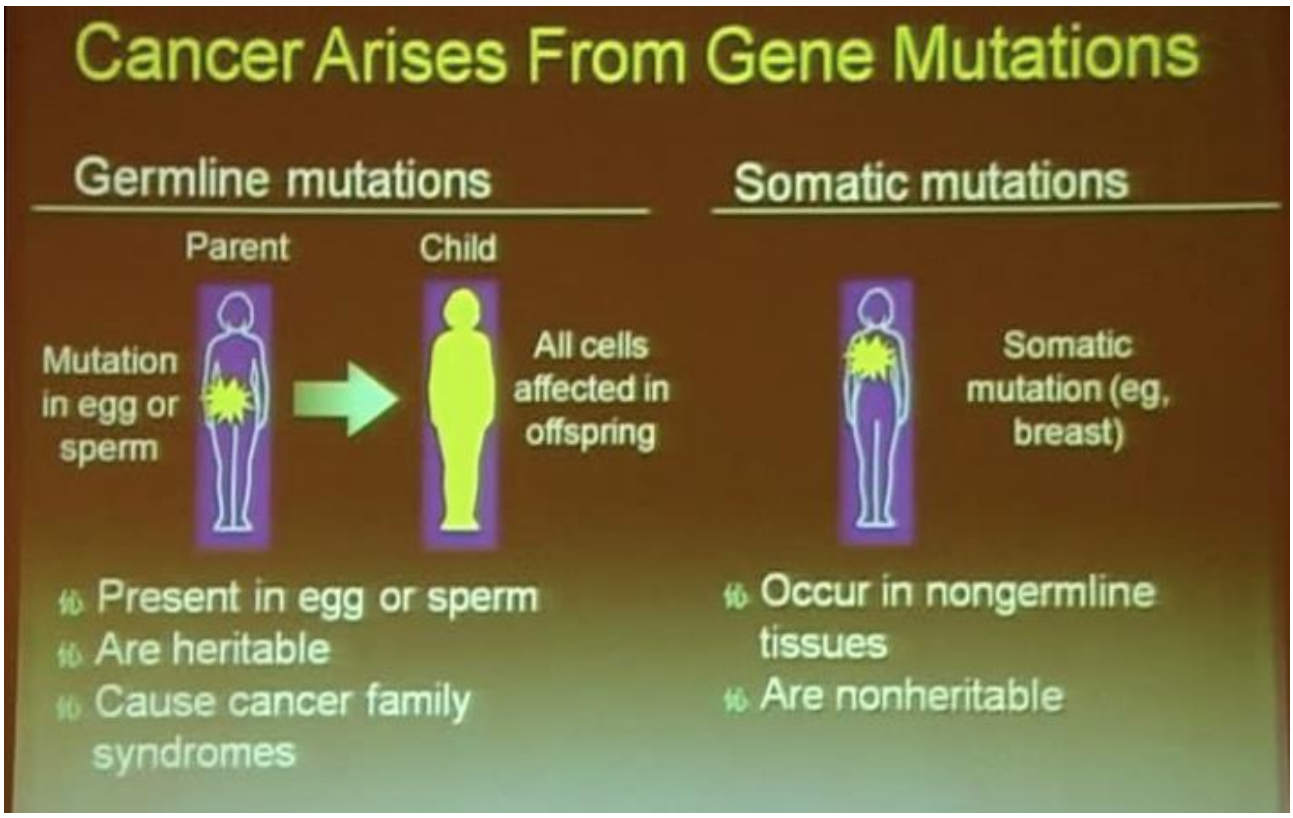
"Cancer is, in essence, A Genetic disease"

What genes are mutated in cancers ?

- Genes that directly control cellular proliferation (rate of cell birth or cell death) : Gate keeper

  Oncogenes

  Tumor suppressor genes
- Genes that do not directly control cell growth, but instead control the rate of mutation
- Caretaker genes or DNA damage-response genes



Principles of systemic therapy

- Systemic therapy is one of the combined modality programs in the treatment of cancer
- Chemotherapy
- Endocrine therapy (eg breast cancer, prostate cancer)
- Biotherapy (eg interferon-alpha > renal cell carcinoma)
- Molecular-targeted therapy

Cancer CMT

- Development of CMT is started in the 1950s.
- CMT could indeed cure cancer.
- Rationale for integrating cMT into combined modality programs with surgery and RT in early stage of disease.

*started since WWII, biochemical weapon)

- Principle obstacles clinical efficacy of CMT:
  Toxicity to normal tissues (BM suppression)
  Development of cellular drug resistance

Clinical application of CMT

- Primary induction CMT
- Neoadjuvant CMT
- Adjuvant CMT
- Direct instillation into sanctuary sites or site-directed perfusion of specific regions of the body affected by cancer. (Brain cancer via ventricle reservoir)

Primary induction CMT

- Cancers for which there are no other effective tx
- Advanced, metastatic disease
- Clinical end points
  Response rate : complete and partial response
  Progression-free survival
  Overall survival
- Goals : curative intent: CMT-sensitive cancers, palliative intent

Primary induction CMT : curative

- Hodgkin's disease
- non-Hodgkin's disease
- Acute leukemia
- Germ cell tumor
- Curable childhood cancers: ALL, Burkitt's lymphoma, Wilm's tumor, Embryonal rhabdomyosarcoma.

Palliative intent:

- Palliative tumor-related symptoms (such as pain)
- Improve overall quality of life
- Prolong time tumor progression
- Prolong overall survival

Palliative CMT

- Small cell lung cancer
- Bladder cancer
- Breast cancer
- Head and neck cancer
- Nasopharyngeal cancer
- Ovarian cancer

Neoadjuvant CMT

- Administration of CMT to cancer patients with localized disease before local treatments
- Localized cancers for which alternative local therapies exist but less than completely effective

- Advantages:
- Preservation of tumor mass as a biologic marker of chemosensitivity
- Sparing of vital normal organs: larynx, anal sphincter, bladder
- Treating micrometastatic disease

- Clinical end points:
- Response rate
- Progression-free survival
- Overall survival

- Applicable in :
- Anal cancer
- Bladder cancer
- Breast cancer
- Esophageal
- Head and neck
- Non small cell lung cancer
- Osteogenic sarcoma
- Rectal cancer
- Soft tissue sarcoma

Adjuvant CMT

- Development of disease recurrence, either locally or systemically, after surgery or radiation or both
- Presence and spreading of occult micrometastais
- Rationale: to treat micrometastatic disease at time when tumor burden is a minimum, enhance potential efficacy of drug treatment.
- Several well-conducted randomized phase III clinical studies have documented the effectiveness of adjuvant CMT in prolonging both disease-free and overall survival in cancer patients.

- Clinical end points:
- Disease-free survival
- Overall survival
- Applicable in :
- Breast cancer
- Colorectal cancer
- Gastric cancer
- Non small cell lung cancer
- Ovarian cancer
- Osteogenic sarcoma
- Testicular cancer
- Malignant glioma : GBM

Principles governing the use of CMT

- Sequential use of drug combinations:
  Norton-Simon model: no two combinations were likely to be non-cross-resistant or have equal cell killing capacity
- Optimal dose and schedule
  Maximal-tolerated dose
  Shortest possible time necessary for recovery of bone marrow
- Optimal duration of administration
- Right indication
- Right patient : adequate organ function, pre-existing condition, performance status

Molecular targeted therapy

- Approved EGFR-targeted therapies
- Trastuzumab (Herceptin) : ErbB-2 monoclonal Ab for breast cancer
- Cetuximab (Erbitux) : EGFR monoclonal Ab for colorectal cancer and HNSCC (kras gene indicate drug resistant or not)
- Gefitinib (Iressa): EGFR tyrosine kinase inhibitor for non small cell lung cancer
- Erlotinib (Tarceva): EGFR tyrosine kinase inhibitor for non small cell lung cancer
- Approved molecular-targeted therapies
- Receptor tyrosine kinase inhibitor: imatinib
- CML
- GIST (c-kit positive ถึงจะใช้ยาตัวนี้ได้)
- Anti VEGF : Bevacizumab : colorectal can, non-small cell lung ca
- Multi-kinase inhibitors :
  Suitinib > GIST after failure to imatinib, renal cell carcinoma
  Sorafinib : renal cell carcinoma, HCC