

腎臟細胞癌AJCC分期及臨床應用

The 7th AJCC Staging System and Clinical Application of Renal Cell Carcinoma

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Content

- # Introduction of AJCC TNM staging system
- # Introduction of renal cell carcinoma
- # Basic anatomy of kidneys
- # 7th AJCC TNM staging system in RCC

What is the AJCC?



- # The American Joint Committee on Cancer (AJCC) established the way cancer is communicated.
- # AJCC cancer staging system provides evidence-based anatomic staging with new breakthroughs in oncologic, radiologic, pathologic and molecular science to understand cancer and treat patients.
- # These AJCC publications are recognized as the authoritative guides for cancer staging information and are used by tens of thousands of medical professionals everyday.








AJCC Publishing History



Publishing History

Editions of the AJCC *Cancer Staging Manual*

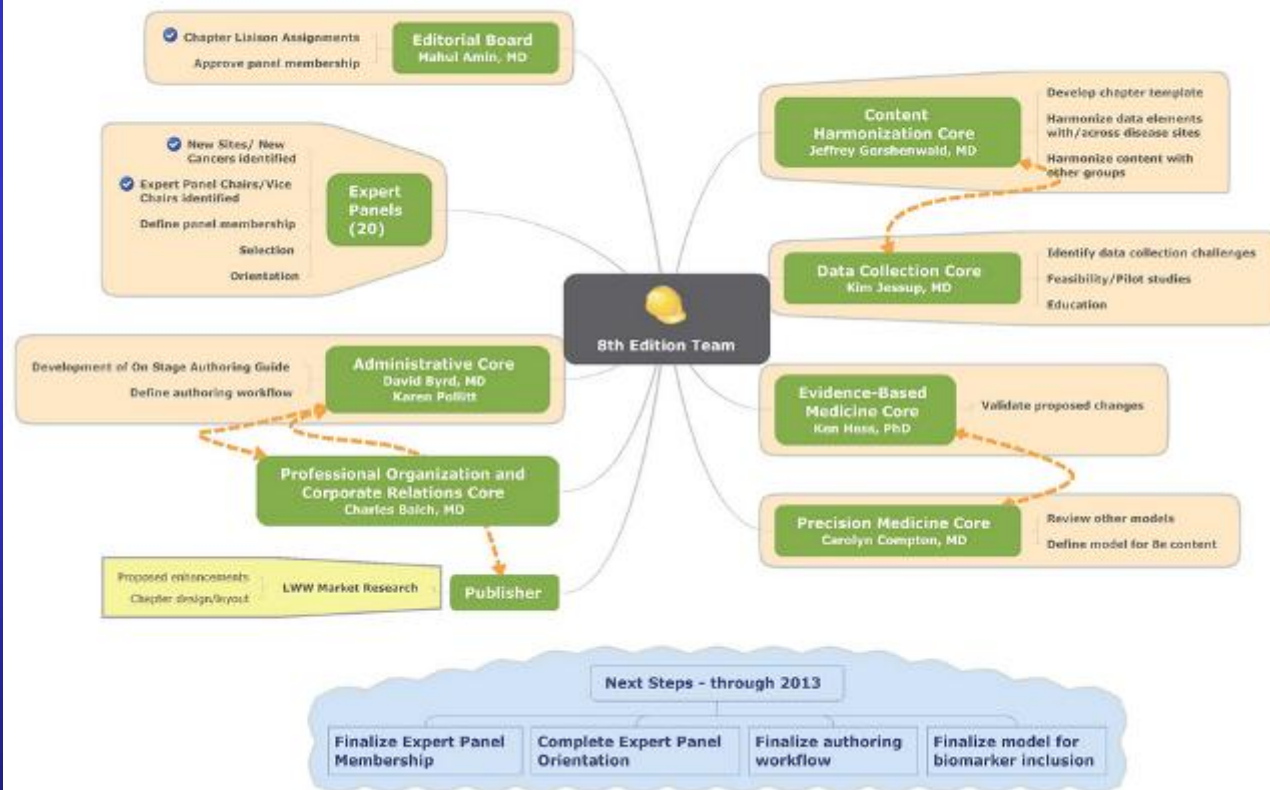
The publication dates and effective dates for past editions of the AJCC Cancer Staging Manual are:

Edition	Publication Year	Effective Year	Resources
1	1977	1978	 AJCC 1st Ed Cancer Staging Manual
2	1983	1984	 AJCC 2nd Ed Cancer Staging Manual
3	1988	1989	 AJCC 3rd Ed Cancer Staging Manual
4	1992	1993	 AJCC 4th Edition Cancer Staging Manual
5	1997	1998	 AJCC 5th Ed Cancer Staging Manual
6	2002	2003	 AJCC 6th Ed Cancer Staging Manual Part 1  AJCC 6th Ed Cancer Staging Manual Part 2
7	2009	2010	Purchase Here
8	2016 (projected)	2017 (projected)	Progress Updates

AJCC 8th Edition Updates

Led by **Mahul B. Amin**, MD, FCAP, the 15 member Editorial Board features representatives from each cancer specialty, and leaders of internal development “cores”- a new concept introduced by Dr. Amin

8th Edition Development Team



What is the TNM Staging System

The TNM Staging System was developed and is maintained by the AJCC and the Union for International Cancer Control (UICC).

The T category: the original (primary) tumor.

TX- Primary tumor cannot be evaluated

T0- No evidence of primary tumor

Tis- Carcinoma in situ (early cancer that has not spread to neighboring tissue)

T1–T4- Size and/or extent of the primary tumor

The N category: whether or not the cancer has reached nearby lymph nodes

NX- Regional lymph nodes cannot be evaluated

N0- No regional lymph node involvement (no cancer found in the lymph nodes)

N1-N3- Involvement of regional lymph nodes (number and/or extent of spread)

The M category: whether there are distant metastases

M0- No distant metastasis

M1- Distant metastasis

TNM Stage Groupings

- **Primary TNM groupings are purely clinical or pathologic (cTNM or pTNM)**
 - **Clinical stage: essential to select and evaluate therapy options**
 - Patients stage **BEFORE** treatment starts
 - Basis for **FIRST** treatment choice
 - **Pathologic stage: provides most precise data to estimate prognosis, plan subsequent therapy, and calculate end results**

Clinical Stage is important

- It is essential to selecting primary therapy
- It should be coded in all cases
- It is based on evidence acquired before the initiation of primary treatment (definitive surgery, or neoadjuvant radiation or systemic therapy)
- **Should NOT be changed** based on subsequent information from treatment, such as:
 - The pathologic examination of resected tissue
 - Information after initiation of definitive therapy

Pathologic Stage is

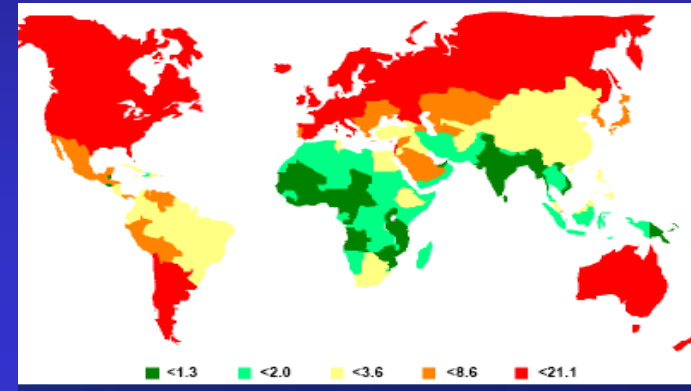
- based on evidence acquired before treatment supplemented and modified by the additional evidence acquired during and from surgery, particularly from **pathologic examination of resected tissues**.
- Cases with pathologic T and N may be grouped as pathologic TNM using clinical M designator (cM0 or cM1)

TNM Stage Classification

- **Stage may be defined at several points in the care of the cancer patient**
 - Pretreatment/clinical stage (cTNM)
 - Pathologic stage (pTNM)
 - After therapy, either before surgery (neoadjuvant) or without surgery (yTNM)
 - Time of recurrence or progression (rTNM)
 - Time of autopsy (aTNM)

Renal Cell Carcinoma: Epidemiology

- * Renal cell carcinoma (RCC) is the most common kidney cancer, representing **2–3% (15th)** of all cancers worldwide¹
- * Annual incidence of RCC worldwide: ~209,000^{2,3}
- * Annual incidence of RCC in Europe: ~40,000⁴
- * Annual mortality rate worldwide: >102,000^{2,3}
- * **20–30%** of patients have metastatic disease at diagnosis⁵
- * Approximately **30%** of patients have recurrence of RCC following resection of localised disease⁶
- * Five-year survival in patients with metastatic disease is typically **<11%**⁶



¹Ljungberg B, et al. *Eur Urol* 2007;51:1502–1510

²Parkin DM, et al. *CA Cancer J Clin* 2005;55:74–108

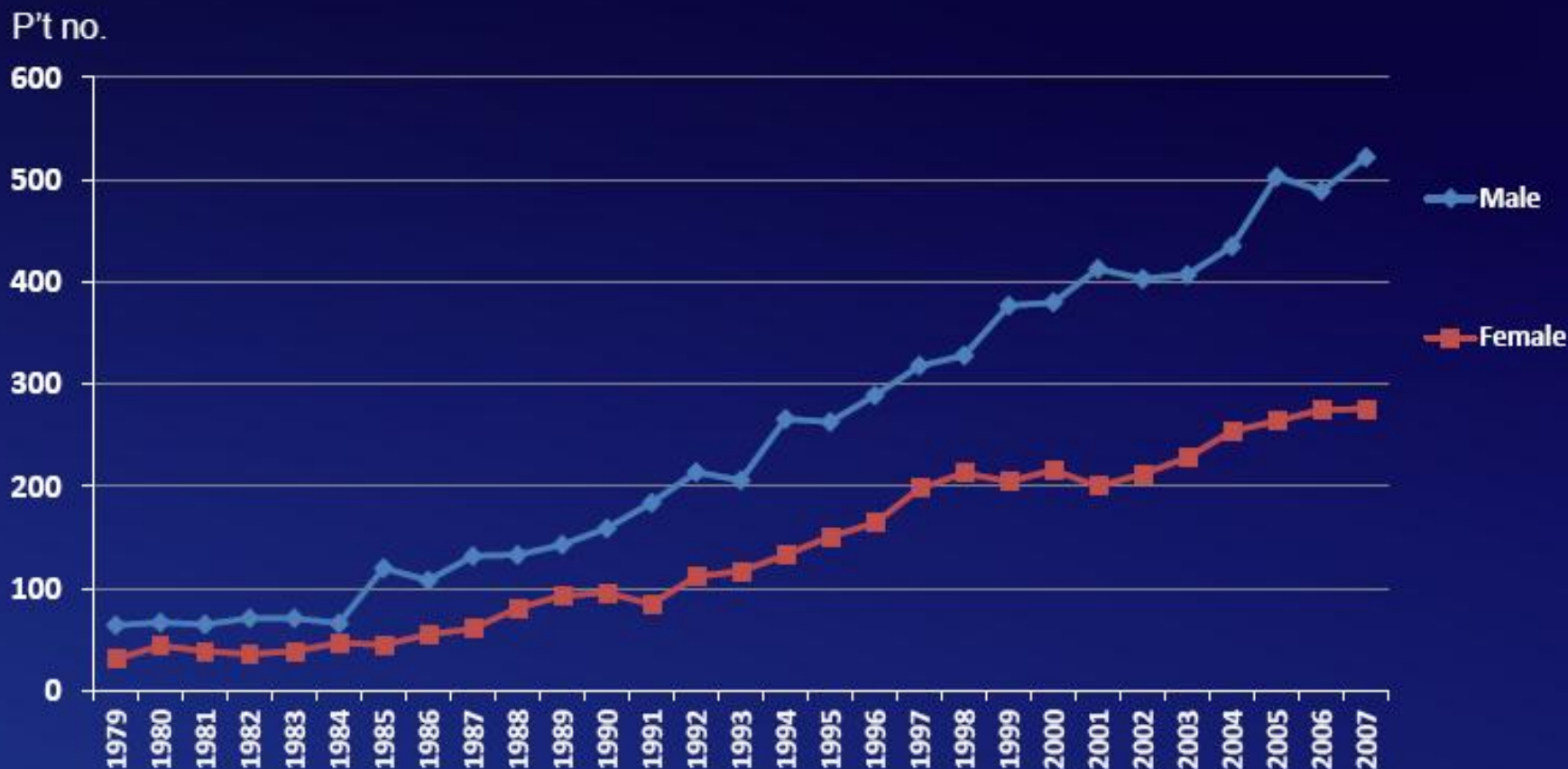
³Vogelzang NJ, Stadler WM. *Lancet* 1998;352:1691–1696

⁴Schöffski P, et al. *Ann Oncol* 2006;17:1185–1196

⁵Godley P, Taylor M. *Curr Opin Oncol* 2001;13:199–203

⁶Zisman A, et al. *J Clin Oncol* 2002;20:4559–4566

Renal cancer trend in Taiwan



Trend for renal cancer in Taiwan:1979-2007

Year	1979	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	
M	N	64	67	65	71	71	66	120	108	132	133	143	159	184	214	206	266	263	289	318	328	377	380	413	403	407	435	503	489	522
	CR	0.70	0.72	0.69	0.74	0.73	0.67	1.20	1.07	1.29	1.29	1.37	1.51	1.73	1.99	1.90	2.44	2.39	2.61	2.85	2.92	3.33	3.34	3.61	3.51	3.53	3.77	4.35	4.22	4.50
	ADJR	0.90	0.85	0.79	0.90	0.81	0.64	1.37	1.26	1.51	1.54	1.56	1.73	1.93	2.18	2.08	2.60	2.54	2.72	2.99	3.00	3.33	3.28	3.50	3.26	3.31	3.33	3.82	3.67	3.76
F	N	31	44	39	36	39	47	45	55	61	81	93	96	85	112	117	133	151	164	198	213	205	216	200	212	228	254	264	275	276
	CR	0.37	0.51	0.45	0.41	0.43	0.51	0.48	0.59	0.64	0.84	0.96	0.97	0.85	1.11	1.15	1.29	1.46	1.57	1.87	1.99	1.90	1.98	1.82	1.92	2.06	2.28	2.36	2.44	2.43
	ADJR	0.46	0.68	0.43	0.49	0.43	0.48	0.55	0.72	0.72	0.98	1.09	1.14	0.99	1.30	1.32	1.46	1.62	1.73	1.97	2.09	1.93	1.97	1.79	1.80	1.85	2.06	2.03	2.03	2.02

N : New case

CR : coarse incidence rate

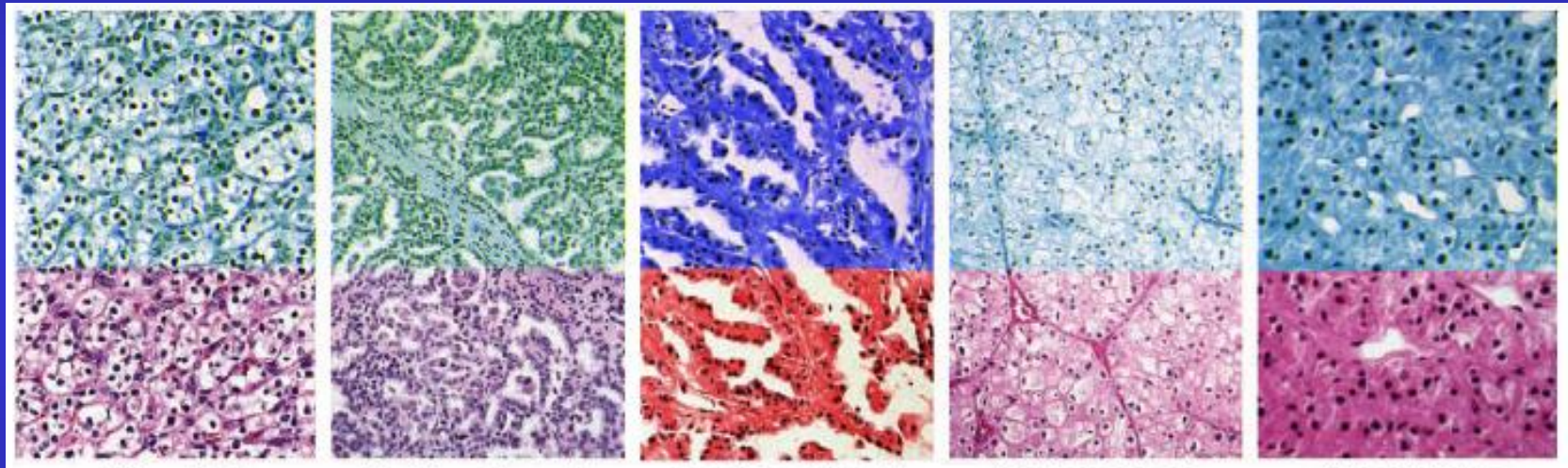
ADJR : adjusted incidence rate in 100,000

Taiwan RCC Number is Growing Up Between 2003-2010



RCC: Histologic Subtypes

Clear-cell tumors are the most common histologic type and represent approximately **75%** of all RCCs

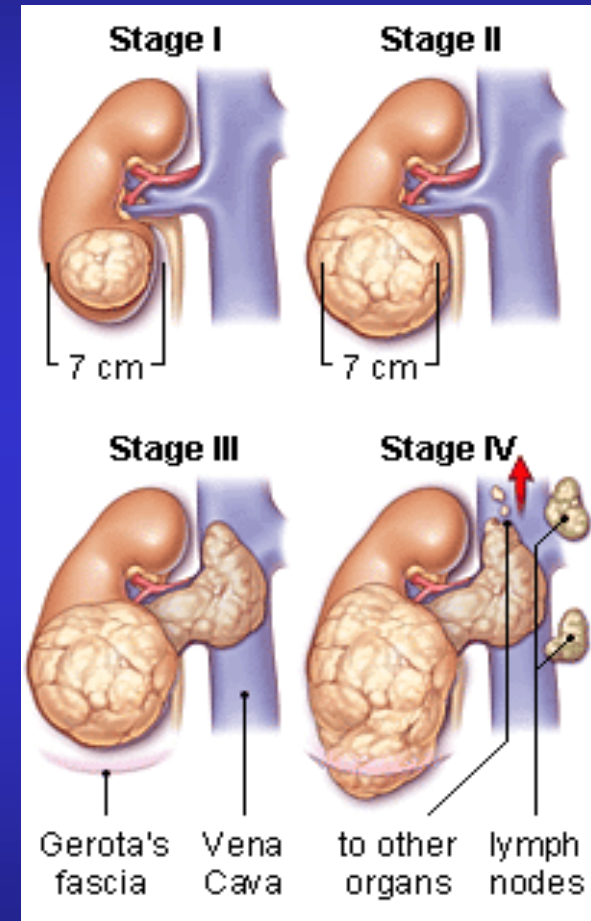


Type	Clear cell	Papillary type 1	Papillary type 2	Chromophobe	Collecting duct carcinoma
Frequency	75%	5%	10%	5%	5%
Gene	VHL	c-Met	FH	BHD	

BHD = Birt-Hogg-Dubé
 FH = Fumarate-hydratase
 VHL = Von-Hippel-Lindau

Renal Cell Carcinoma (RCC) Overview

- # RCC is classified into 5 main types of tumors
Clear-cell tumors – most common histologic type
- # Primary management of localized disease is surgical resection
- # **33%** exhibit distant metastases at initial diagnosis
- # Limited treatment options in the pre-targeted therapy era
- # Based on **MSKCC criteria/Heng criteria**, patients are divided into good, intermediate and poor risk group

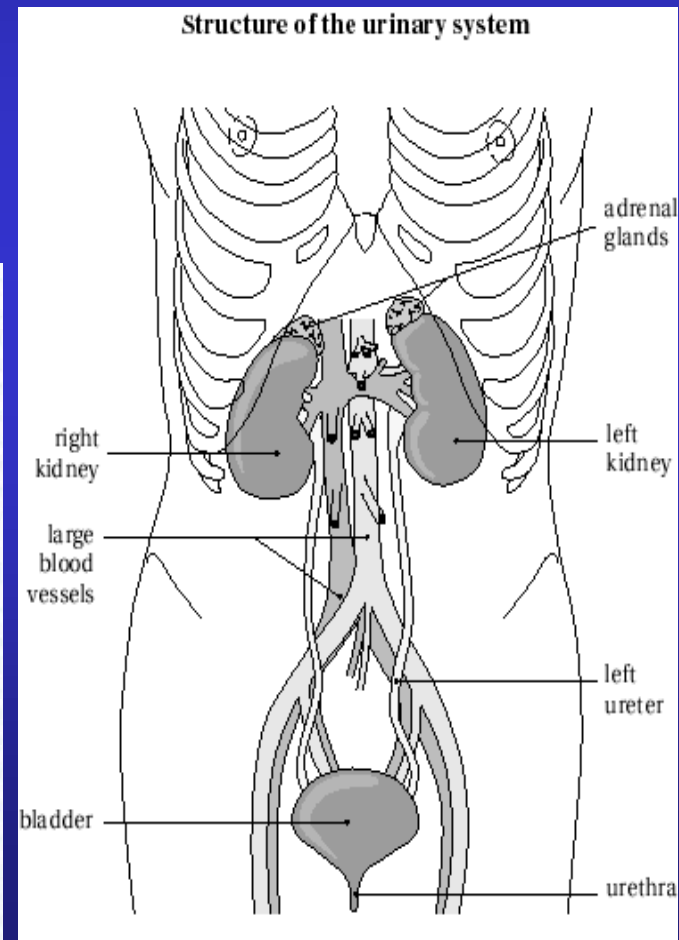
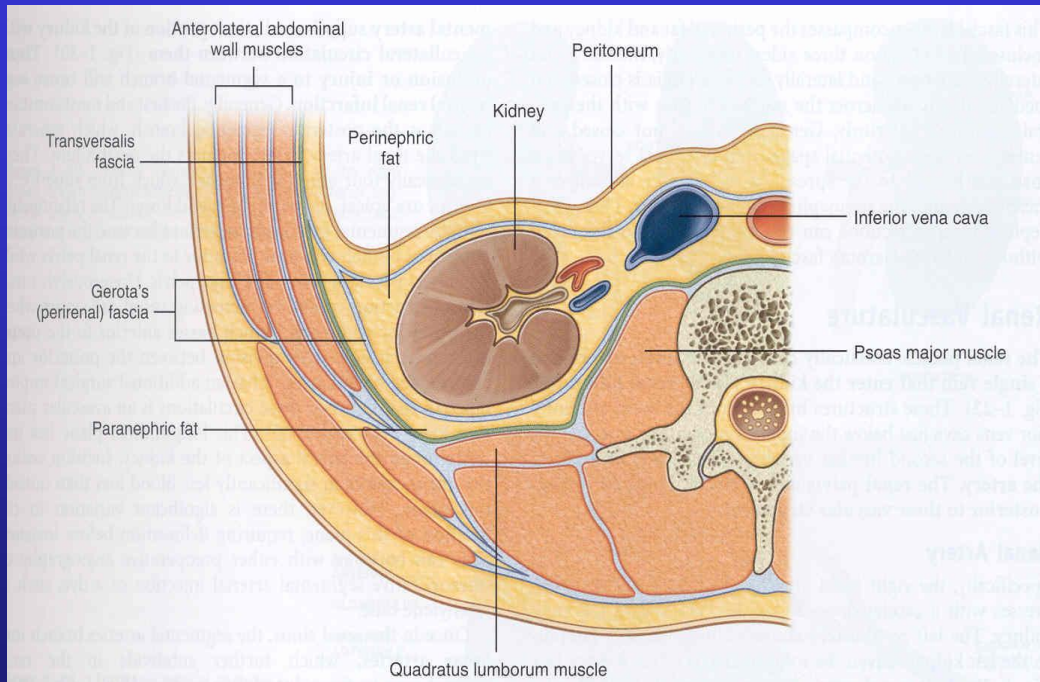


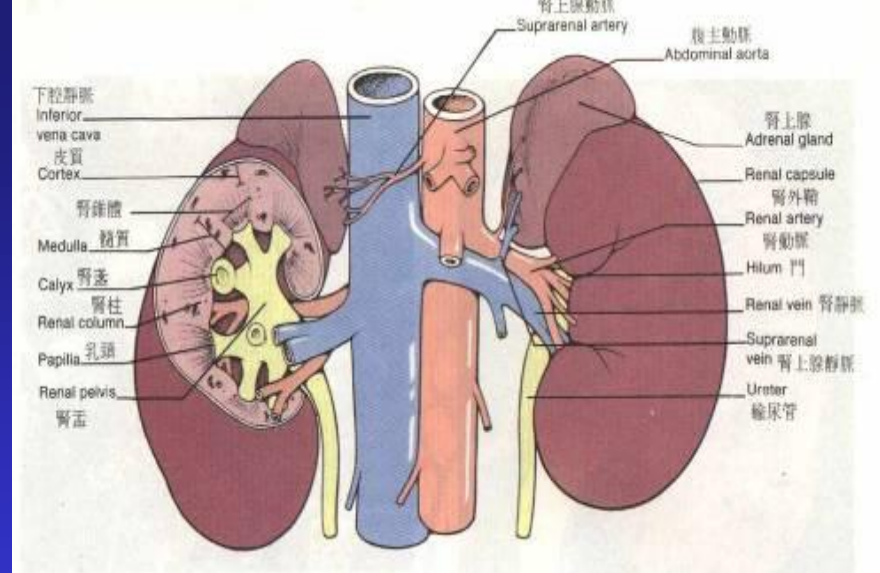
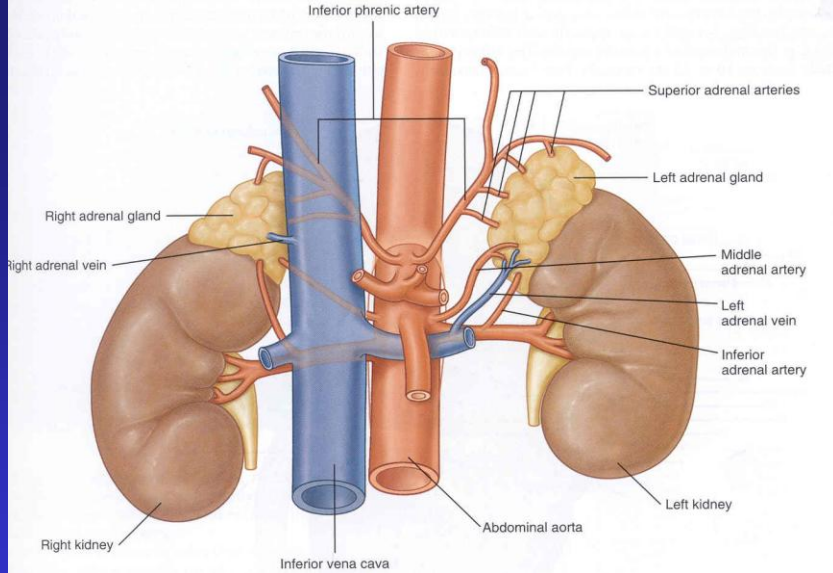
Anatomy of Kidney

位於脊柱兩側，腹腔後壁稍高的凹陷處(**retroperitoneal position**), 上下緣分別為上緣：第十一胸椎(T11) 下緣：第三腰椎(L3)

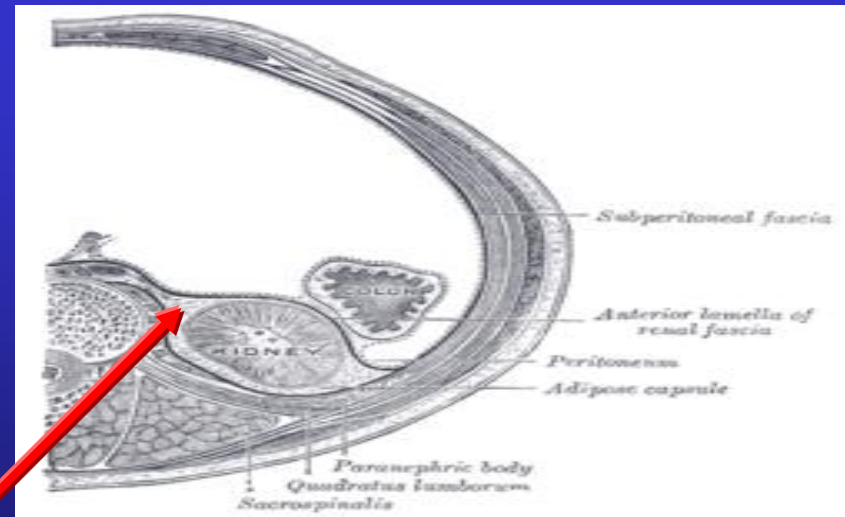
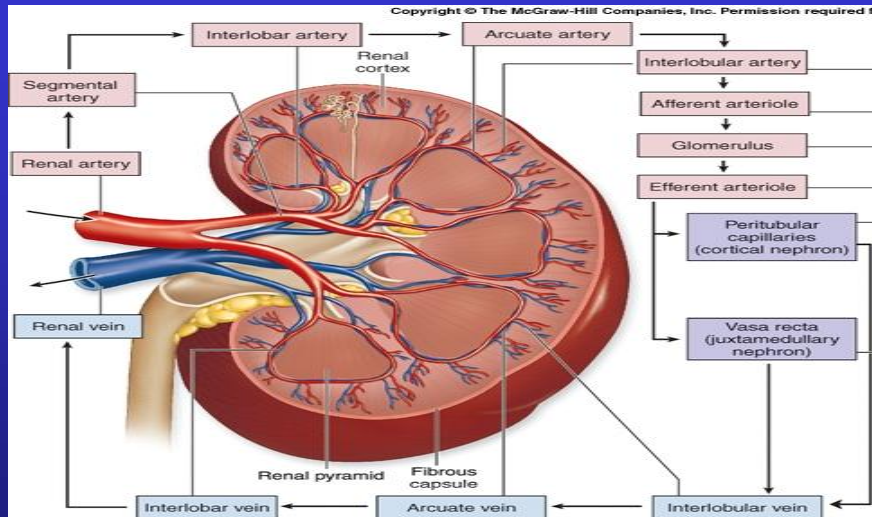
會隨運動姿勢或呼吸而有改變

狀如蠶豆, 左腎比右腎高約1.5-2公分





外側為凸面，內側凹陷，造成一空腔-腎竇(renal sinus)/ 腎門 (renal hilum), 許多血管、神經、淋巴管和輸尿管由此處通過



The renal fascia or **Gerota's fascia** is a layer of connective tissue encapsulating the kidneys and the suprarenal glands.

7th AJCC TNM stage of RCC

CLINICAL <i>Extent of disease before any treatment</i>	STAGE CATEGORY DEFINITIONS		PATHOLOGIC <i>Extent of disease through completion of definitive surgery</i>
<input type="checkbox"/> y clinical – staging completed after neoadjuvant therapy but before subsequent surgery	TUMOR SIZE: _____	LATERALITY: <input type="checkbox"/> left <input type="checkbox"/> right <input type="checkbox"/> bilateral	<input type="checkbox"/> y pathologic – staging completed after neoadjuvant therapy AND subsequent surgery
PRIMARY TUMOR (T)			
<input type="checkbox"/> TX	Primary tumor cannot be assessed		<input type="checkbox"/> TX
<input type="checkbox"/> T0	No evidence of primary tumor		<input type="checkbox"/> T0
<input type="checkbox"/> T1	Tumor 7 cm or less in greatest dimension, limited to the kidney		<input type="checkbox"/> T1
<input type="checkbox"/> T1a	Tumor 4 cm or less in greatest dimension, limited to the kidney		<input type="checkbox"/> T1a
<input type="checkbox"/> T1b	Tumor more than 4 cm but not more than 7 cm in greatest dimension limited to the kidney		<input type="checkbox"/> T1b
<input type="checkbox"/> T2	Tumor more than 7 cm in greatest dimension, limited to the kidney		<input type="checkbox"/> T2
<input type="checkbox"/> T2a	Tumor more than 7 cm but less than or equal to 10 cm in greatest dimension, limited to the kidney		<input type="checkbox"/> T2a
<input type="checkbox"/> T2b	Tumor more than 10 cm, limited to the kidney		<input type="checkbox"/> T2b
<input type="checkbox"/> T3	Tumor extends into major veins or perinephric tissues but not into the ipsilateral adrenal gland and not beyond Gerota's fascia		<input type="checkbox"/> T3
<input type="checkbox"/> T3a	Tumor grossly extends into the renal vein or its segmental (muscle containing) branches, or tumor invades perirenal and/or renal sinus fat but not beyond Gerota's fascia		<input type="checkbox"/> T3a
<input type="checkbox"/> T3b	Tumor grossly extends into the vena cava below the diaphragm		<input type="checkbox"/> T3b
<input type="checkbox"/> T3c	Tumor grossly extends into the vena cava above the diaphragm or invades the wall of the vena cava		<input type="checkbox"/> T3c
<input type="checkbox"/> T4	Tumor invades beyond Gerota's fascia (including contiguous extension into the ipsilateral adrenal gland)		<input type="checkbox"/> T4

1. Bassil B, Dosoretz DE, Prout GR Jr: Validation of the tumor, nodes and metastasis classification of renal cell carcinoma. J Urol 134 (3): 450-4, 1985. 2. Golimbu M, Joshi P, Sperber A, et al.: Renal cell carcinoma: survival and prognostic factors. Urology 27 (4): 291-301, 1986. 3. Robson CJ, Churchill BM, Anderson W: The results of radical nephrectomy for renal cell carcinoma. J Urol 101 (3): 297-301, 1969. 4. Consensus conference. Magnetic resonance imaging. JAMA 259 (14): 2132-8, 1988. 5. Kidney. In: Edge SB, Byrd DR, Compton CC, et al., eds.: AJCC Cancer Staging Manual. 7th ed. New York, NY: Springer, 2010, pp 479-89.

7th AJCC TNM stage of RCC

REGIONAL LYMPH NODES (N)		
<input type="checkbox"/> NX	Regional lymph nodes cannot be assessed	<input type="checkbox"/> NX
<input type="checkbox"/> N0	No regional lymph node metastasis	<input type="checkbox"/> N0
<input type="checkbox"/> N1	Regional lymph node metastasis	<input type="checkbox"/> N1

7th AJCC TNM stage of RCC

DISTANT METASTASIS (M)		
<input type="checkbox"/> M0	No distant metastasis (no pathologic M0; use clinical M to complete stage group)	
<input type="checkbox"/> M1	Distant metastasis	<input type="checkbox"/> M1

PROGNOSTIC FACTORS (SITE-SPECIFIC FACTORS)

REQUIRED FOR STAGING: None

CLINICALLY SIGNIFICANT:

Invasion beyond capsule into fat or perisinus tissues: _____

Venous involvement: _____

Adrenal Extension: _____

Fuhrman Grade: _____

Sarcomatoid features: _____

Histologic tumor necrosis: _____

7th AJCC TNM stage of RCC

ANATOMIC STAGE • PROGNOSTIC GROUPS							
CLINICAL				PATHOLOGIC			
GROUP	T	N	M	GROUP	T	N	M
<input type="checkbox"/> I	T1	N0	M0	<input type="checkbox"/> I	T1	N0	M0
<input type="checkbox"/> II	T2	N0	M0	<input type="checkbox"/> II	T2	N0	M0
<input type="checkbox"/> III	T1 or T2	N1	M0	<input type="checkbox"/> III	T1 or T2	N1	M0
	T3	N0 or N1	M0		T3	N0 or N1	M0
<input type="checkbox"/> IV	T4	Any N	M0	<input type="checkbox"/> IV	T4	Any N	M0
	Any T	Any N	M1		Any T	Any N	M1
<input type="checkbox"/> Stage unknown				<input type="checkbox"/> Stage unknown			

Treatment of Stage I Renal Cell Carcinoma- T1N0M0

- # Surgical resection is the accepted, often curative, therapy for stage I renal cell cancer: partial vs. radical.
- # radical nephrectomy: removal of the kidney, adrenal gland, perirenal fat, and Gerota fascia, with or without a regional lymph node dissection.
- # patients who are not candidates for surgery: external-beam radiation therapy (EBRT) or arterial embolization.
- # patients with bilateral stage I neoplasms (concurrent or subsequent): bilateral partial nephrectomy or unilateral partial nephrectomy with contralateral radical nephrectomy, when technically feasible, may be a preferred alternative to bilateral nephrectomy with dialysis or transplantation.
- # Increasing evidence suggests that a partial nephrectomy is curative in selected cases.
- # Standard treatment options:
 - Radical nephrectomy.[4]
 - Partial nephrectomy (selected patients).[2,4]
 - EBRT (palliative).[4]
 - Arterial embolization (palliative).[4,5]
 - Clinical trials.

Treatment of Stage II Renal Cell Carcinoma- T2N0M0

- # Radical resection is the accepted, often curative, therapy for stage II renal cell cancer. Lymphadenectomy is commonly employed, but its effectiveness has not been definitively proven.
- # External-beam radiation therapy (EBRT) has no conclusive evidence that can improve survival when compared with the results of surgery alone; however, it may be of benefit in selected patients with more extensive tumors. In patients who are not candidates for surgery, arterial embolization can provide palliation.

Standard treatment options:

Radical nephrectomy.[3]

Nephrectomy before or after EBRT (selected patients).[3]

Partial nephrectomy (selected patients).[3]

EBRT (palliative).[3]

Arterial embolization (palliative).

Clinical trials.

Treatment of Stage III Renal Cell Carcinoma- T1/2N1M0; T3N0/1M0

T3a, N0, M0

- Radical resection is the accepted, often curative, therapy for stage III renal cell cancer. Lymphadenectomy is commonly employed. EBRT may be of benefit in selected patients with more extensive tumors. In patients who are not candidates for surgery, arterial embolization can provide palliation.
- In patients with bilateral stage T3a neoplasms (concurrent or subsequent), bilateral partial nephrectomy or unilateral partial nephrectomy with contralateral radical nephrectomy, may be a preferred alternative to bilateral nephrectomy with dialysis or transplantation.[3]

T3b, N0, M0

- Radical resection with extended to remove the entire renal vein and caval thrombus and a portion of the vena cava as necessary.[4] EBRT has been given before or after nephrectomy in patients who are not candidates for surgery, arterial embolization can provide palliation.

Treatment informations of following classifications:

T1, N1, M0; T2, N1, M0; T3, N1, M0

This stage of renal cell cancer is curable with surgery in a small minority of cases. A radical nephrectomy and lymph node dissection is necessary. Arterial embolization of the tumor with gelfoam or other materials may be employed preoperatively to reduce blood loss at nephrectomy or for palliation in patients with inoperable disease.

Treatment of Stage III Renal Cell Carcinoma- T1/2N1M0; T3N0/1M0

Standard treatment options:

Radical nephrectomy with renal vein and, as necessary, vena caval resection (for T3b tumors).[4] Radical nephrectomy with lymph node dissection.

Preoperative embolization and radical nephrectomy.[7,8]

EBRT (palliative).[7]

Tumor embolization (palliative).[8]

Palliative nephrectomy.

Preoperative or postoperative EBRT and radical nephrectomy.[7]

Clinical trials involving adjuvant interferon-alpha.

1. Kidney. In: Edge SB, Byrd DR, Compton CC, et al., eds.: AJCC Cancer Staging Manual. 7th ed. New York, NY: Springer, 2010, pp 479-89. 2. Phillips E, Messing EM: Role of lymphadenectomy in the treatment of renal cell carcinoma. Urology 41 (1): 9-15, 1993. 3. Novick AC, Strem SB, Montie JE, et al.: Conservative surgery for renal cell carcinoma: a single-center experience with 100 patients. J Urol 141 (4): 835-9, 1989. 4. Hatcher PA, Anderson EE, Paulson DF, et al.: Surgical management and prognosis of renal cell carcinoma invading the vena cava. J Urol 145 (1): 20-3; discussion 23-4, 1991. 5. deKernion JB: Management of renal adenocarcinoma. In: deKernion JB, Paulson DF, eds.: Genitourinary Cancer Management. Philadelphia, Pa: Lea and Febiger, 1987, pp 187-217. 6. Angermeier KW, Novick AC, Strem SB, et al.: Nephron-sparing surgery for renal cell carcinoma with venous involvement. J Urol 144 (6): 1352-5, 1990. 7. deKernion JB, Berry D: The diagnosis and treatment of renal cell carcinoma. Cancer 45 (7 Suppl): 1947-56, 1980. 8. Swanson DA, Wallace S, Johnson DE: The role of embolization and nephrectomy in the treatment of metastatic renal carcinoma. Urol Clin North Am 7 (3): 719-30, 1980.

Treatment of Stage IV Renal Cell Carcinoma- T4, anyNM0; anyT, anyN, M1

Almost all patients with stage IV renal cell cancer are incurable.

Local Therapy: Tumor embolization, external-beam radiation therapy (EBRT), and nephrectomy can aid in the palliation of symptoms caused by the primary tumor or related ectopic hormone or cytokine production.

Cytokine Therapy:

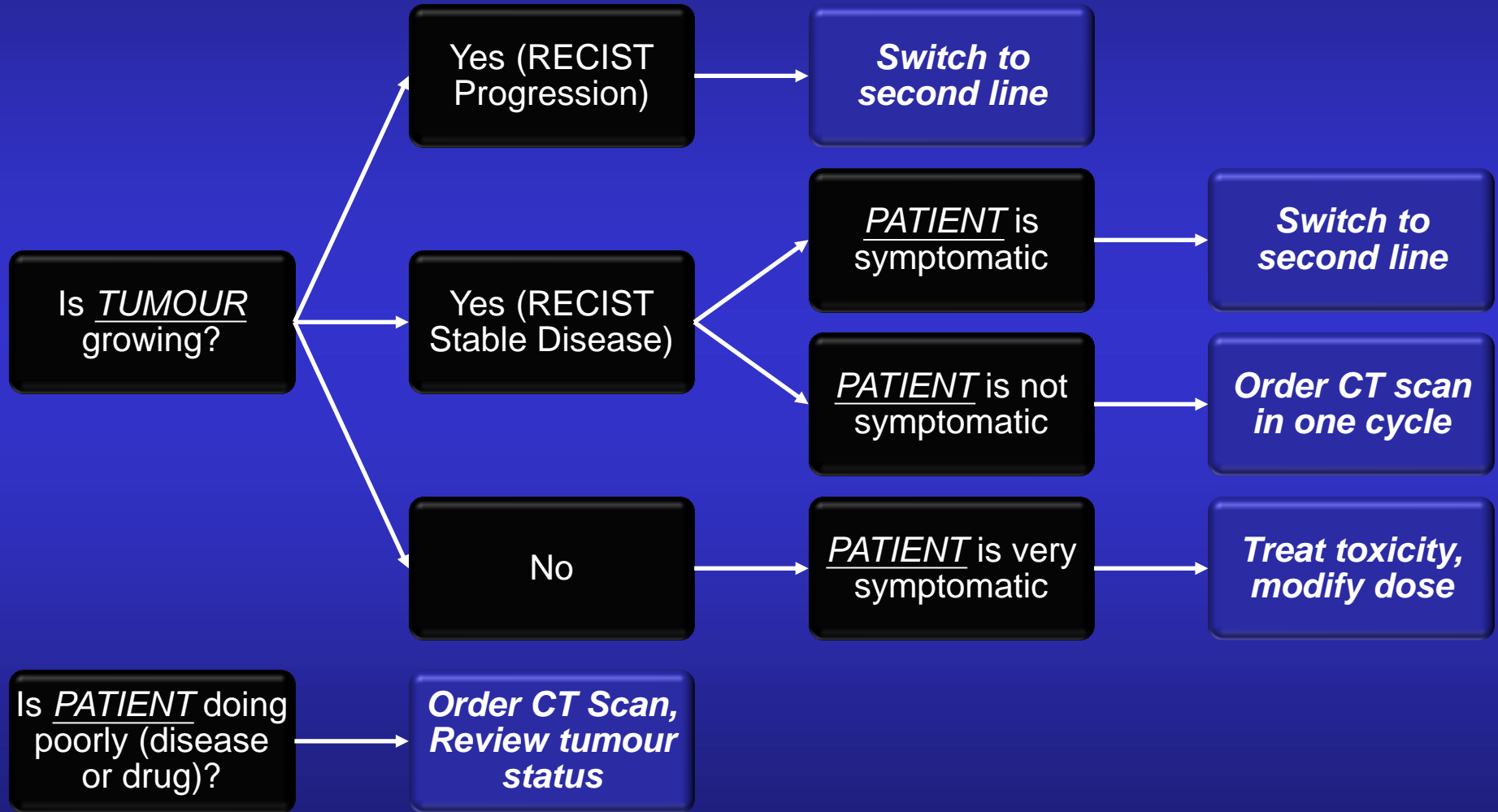
- Cytokine therapy with interferon-alpha or interleukin-2 (IL-2) has been shown to induce objective responses, and interferon-alpha appears to have a modest impact on survival in selected patients.
- High-dose IL-2 produces a similar overall response rate to interferon-alpha, but approximately 5% of patients had durable complete remissions.^[12-17] IL-2 has never been shown in a randomized, controlled trial to result in longer survival. High-dose IL-2 is used because it is the only systemic therapy that has been associated with inducing durable complete remissions.

Antiangiogenic and Other Targeted Therapy: A growing understanding of the biology of cancer in general, and renal cell carcinoma in particular, has led to the development and U.S. Food and Drug Administration (FDA) approval of six new agents targeting specific growth pathways.

Current First-line mRCC Treatment Recommendations

Setting	Recommended Options	Other Options
MSKCC risk: good or intermediate	<ul style="list-style-type: none">• Sunitinib• Bevacizumab + IFN• Pazopanib	<ul style="list-style-type: none">• High-dose IL-2• Sorafenib• Clinical trial
MSKCC risk: poor	<ul style="list-style-type: none">• Temsirolimus	<ul style="list-style-type: none">• Sunitinib• Clinical trial

Algorithm Based on Balance Between Patient and Tumour Characteristics



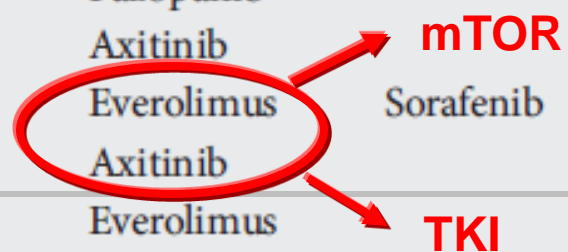
Sequential Targeted Therapy Is the Current Standard of Care for mRCC

Regimen	Setting	Recommended Therapy	Other Options
Treatment-refractory patient (≥2nd line)	Cytokine-refractory	Sorafenib Sunitinib Pazopanib Axitinib	Sunitinib Bevacizumab + IFN-α Temsirolimus Clinical trial
	TKI-refractory	Everolimus Axitinib	Sunitinib Sorafenib Pazopanib Temsirolimus Bevacizumab + IFN-α Clinical trial

1. Escudier B et al. *Ann Oncol*. 2012;23(suppl 7):vii65-vii71.
2. Ljungberg B et al. *Eur Urol*. 2010;58:398-406.
3. de Reijke TM et al. *Eur J Cancer*. 2009;45:765-773.
4. NCCN. Clinical Practice Guidelines in Oncology for Kidney Cancer. V 1.2013.

mRCC Treatment Paradigm

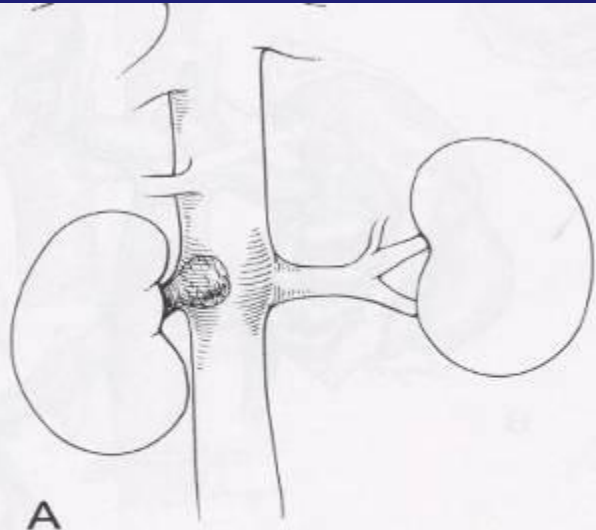
Histology and setting	Risk group	Standard	Option
Clear-cell first line	Good or intermediate risk	Sunitinib Bevacizumab + IFN Pazopanib	Cytokines (including high dose IL2) Sorafenib
	Poor prognosis	Temsirolimus	Sunitinib Sorafenib
Clear-cell <u>second line</u>	Post-cytokines	Sorafenib Pazopanib Axitinib	Sunitinib
	<u>Post-TKIs</u>	Everolimus Axitinib	Sorafenib
Clear-cell third line	Post-2 TKIs	Everolimus	TKI
Non-clear-cell histology			Temsirolimus Sunitinib Sorafenib



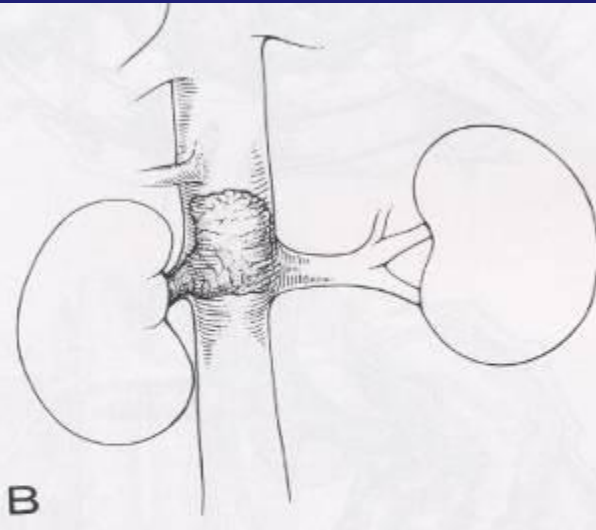
Stage IV Renal Cell Carcinoma- T4, anyNM0; anyT, anyN, M1

Chemotherapy: Responses to cytotoxic chemotherapy generally have not exceeded 10% for any regimen that has been studied in adequate numbers of patients.

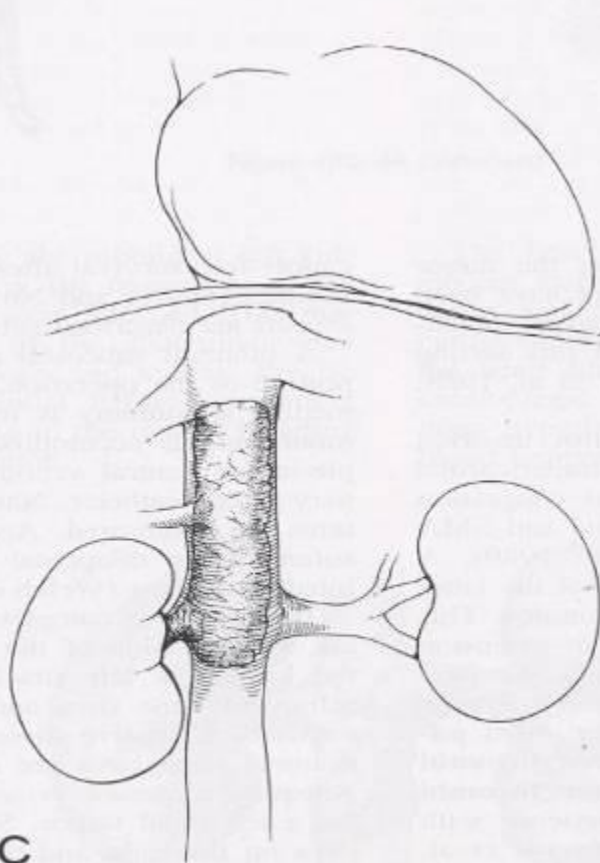
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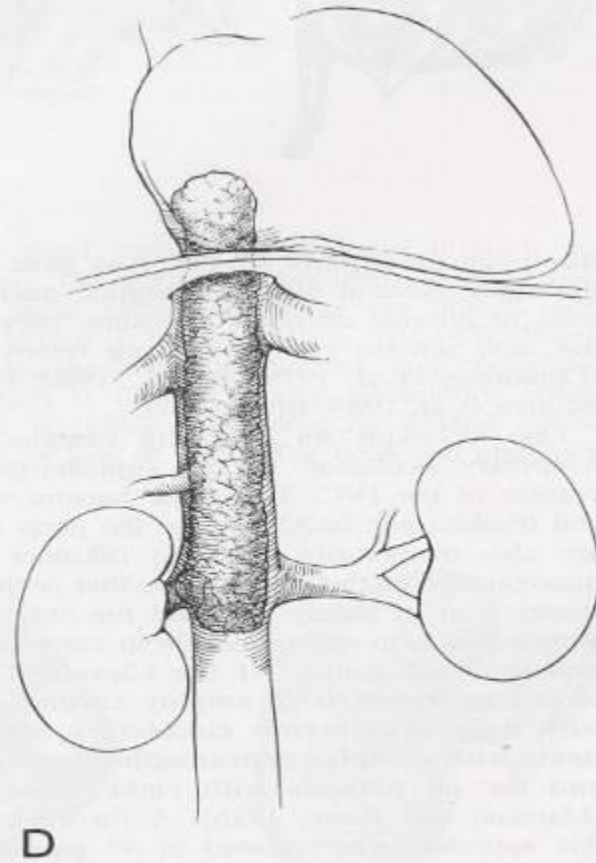
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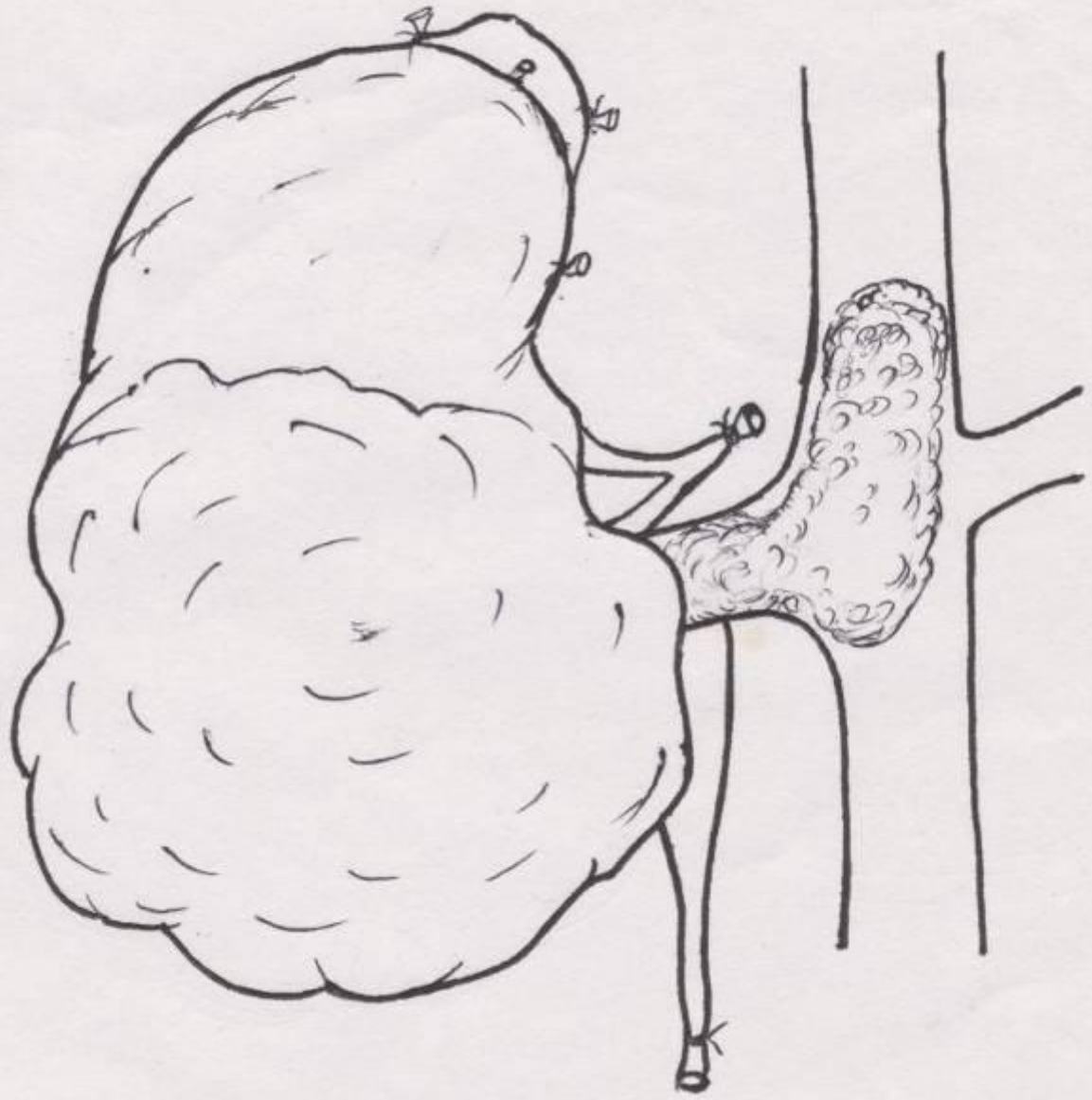
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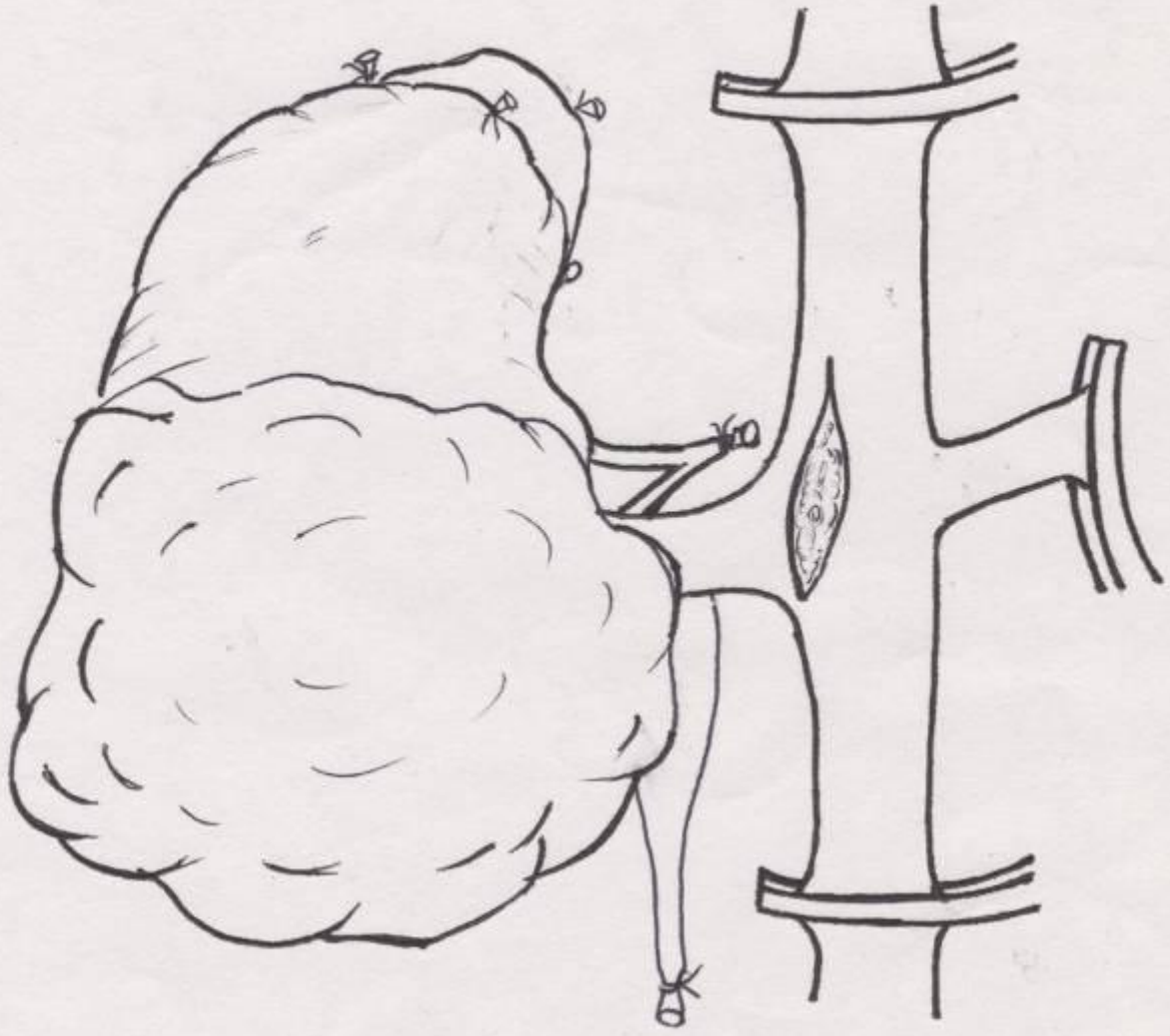


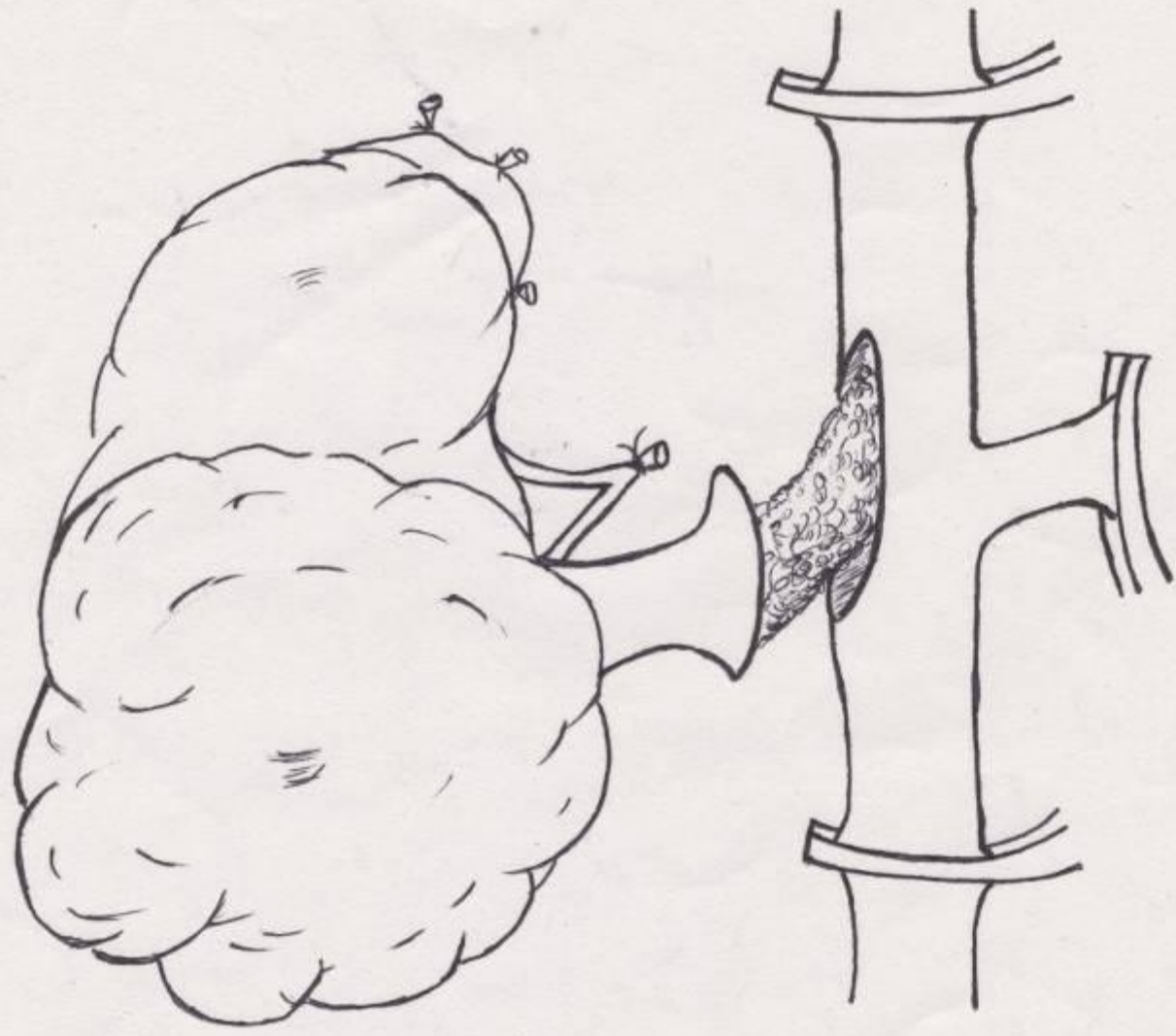
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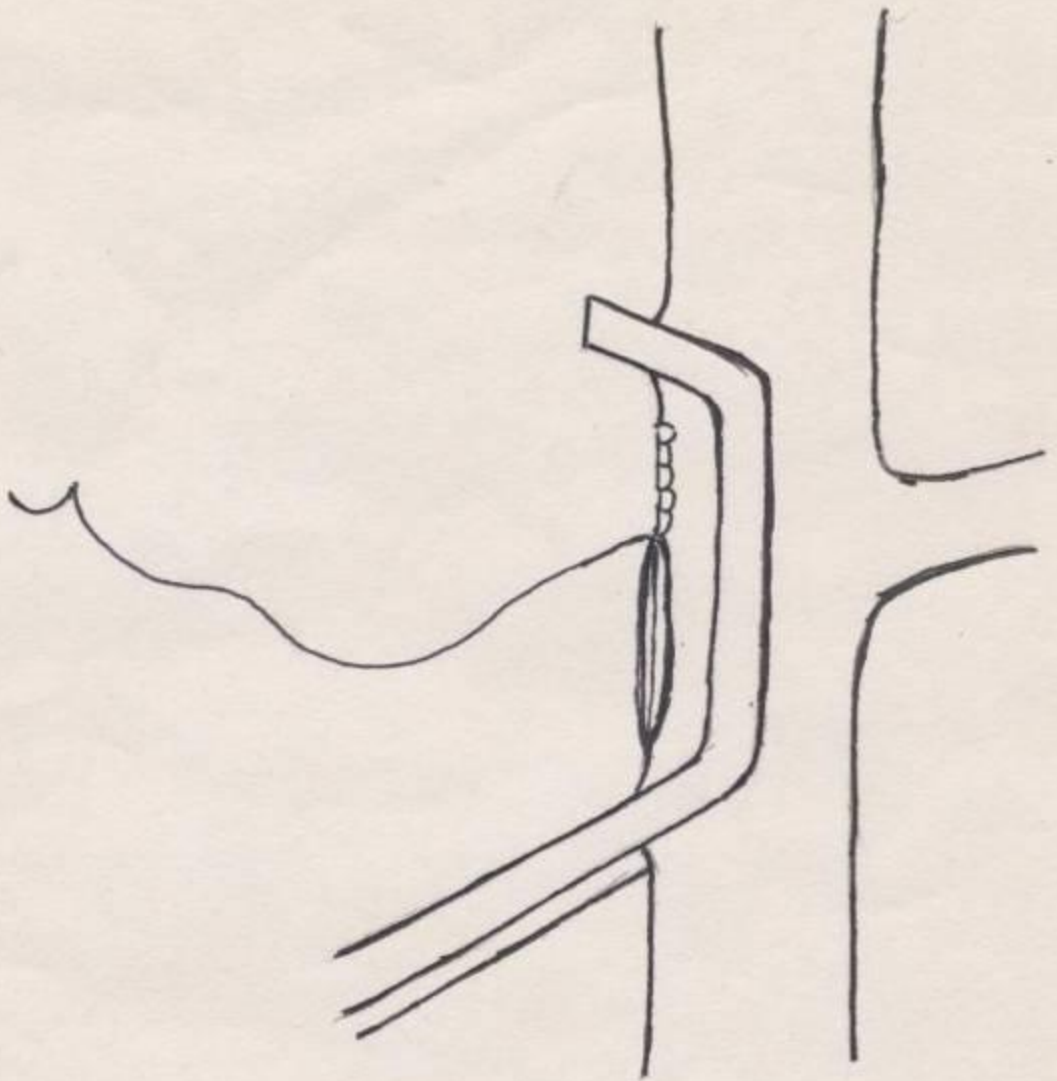


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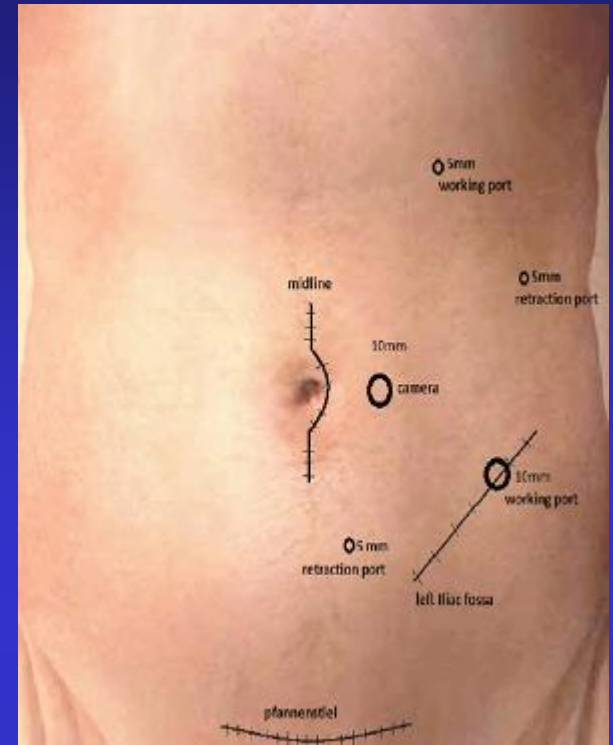
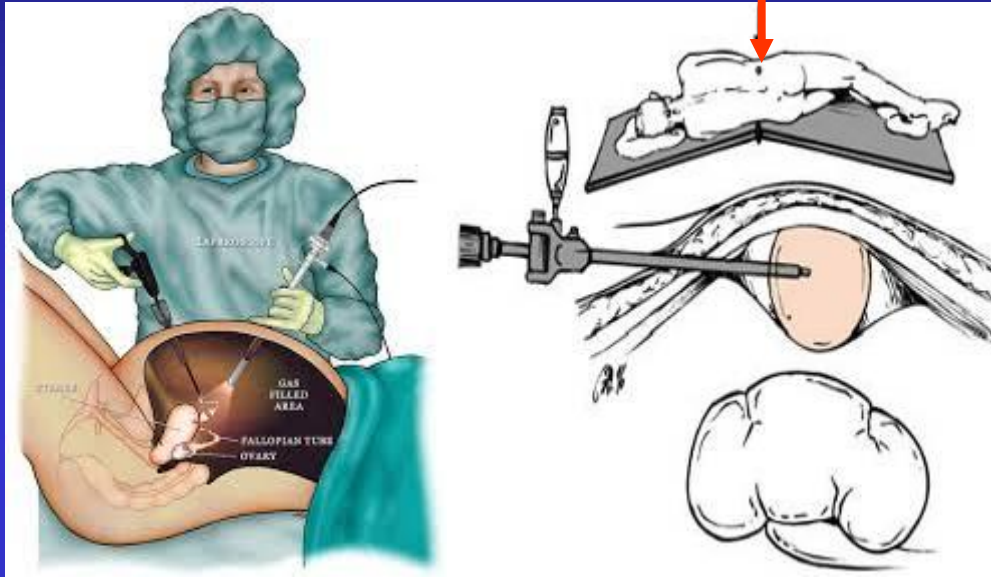






Laparoscopic approach

Retroperitoneoscopic approach



Single port



Mickey Mouse



Hand port

