Timik Malignitelerde Multimodal Yaklaşım

Dr. Yeşim Eralp

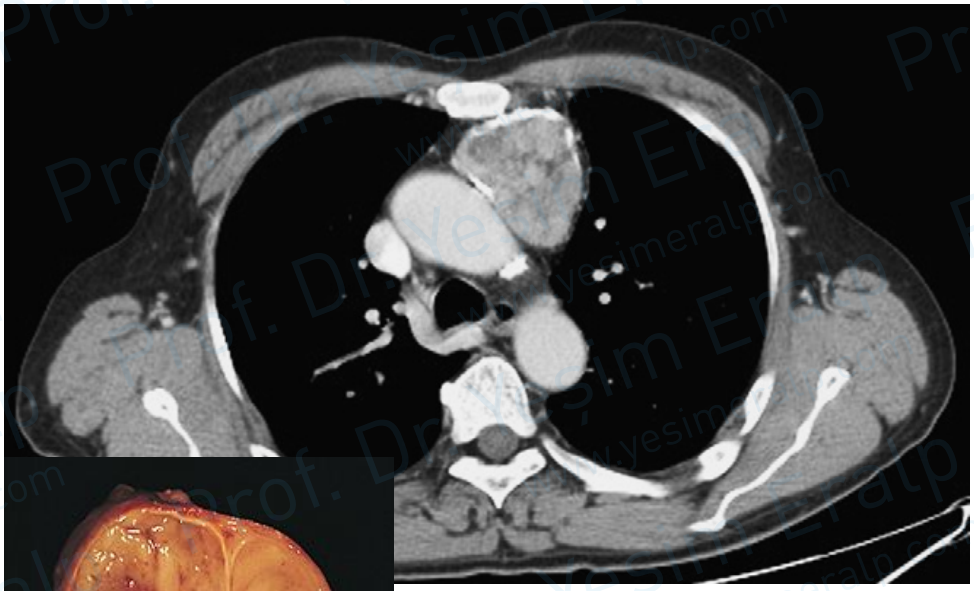
ITMIG Yeni Evreleme: Masaoka-Koga Sistemi

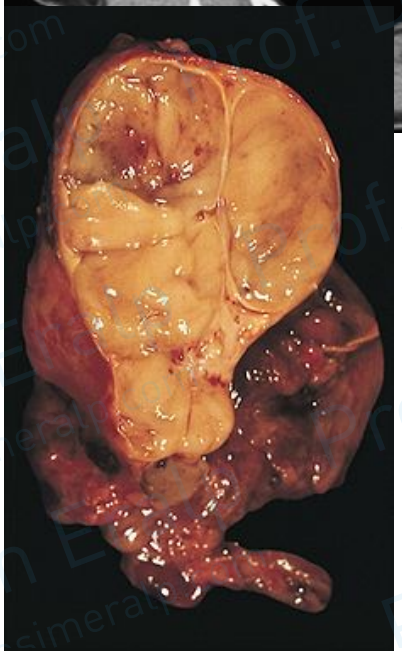
Tumor stage		Description
I		Grossly and microscopically completely encapsulated tumor
II	a	Microscopic transcapsular invasion
	b	Macroscopic invasion into thymic or surrounding fatty tissue, or grossly adherent but not breaking through mediastinal pleura or pericardium
III		Macroscopic invasion of neighboring organs (pericardium, great vessels or lung)
IV	a	Pleural or pericardial dissemination
IV	b	Lymphatic or hematogenous metastasis

Tumors with invasion into but not through the capsule or: Tumors in which the capsule is missing, but without invasion into the surrounding organs/structures

Microscopic involvement of the pericardium (either partial in the fibrous layer or penetrating through the serosal layer) or:
Microscopically confirmed direct penetration into the outer elastin layer of the visceral pleura or into the lung parenchyma, or:
Invasion into the phrenic or vagus nerves (microscopically confirmed, since adhesion is not sufficient) or:
Invasion into or penetration through major vascular structures (microscopically confirmed) or:
Adherence (i.e. fibrous attachment) of lung or adjacent organs only if there is mediastinal pleura or pericardial invasion (microscopically confirmed)

Filosso Lung Cancer 83 (2014) 126–132





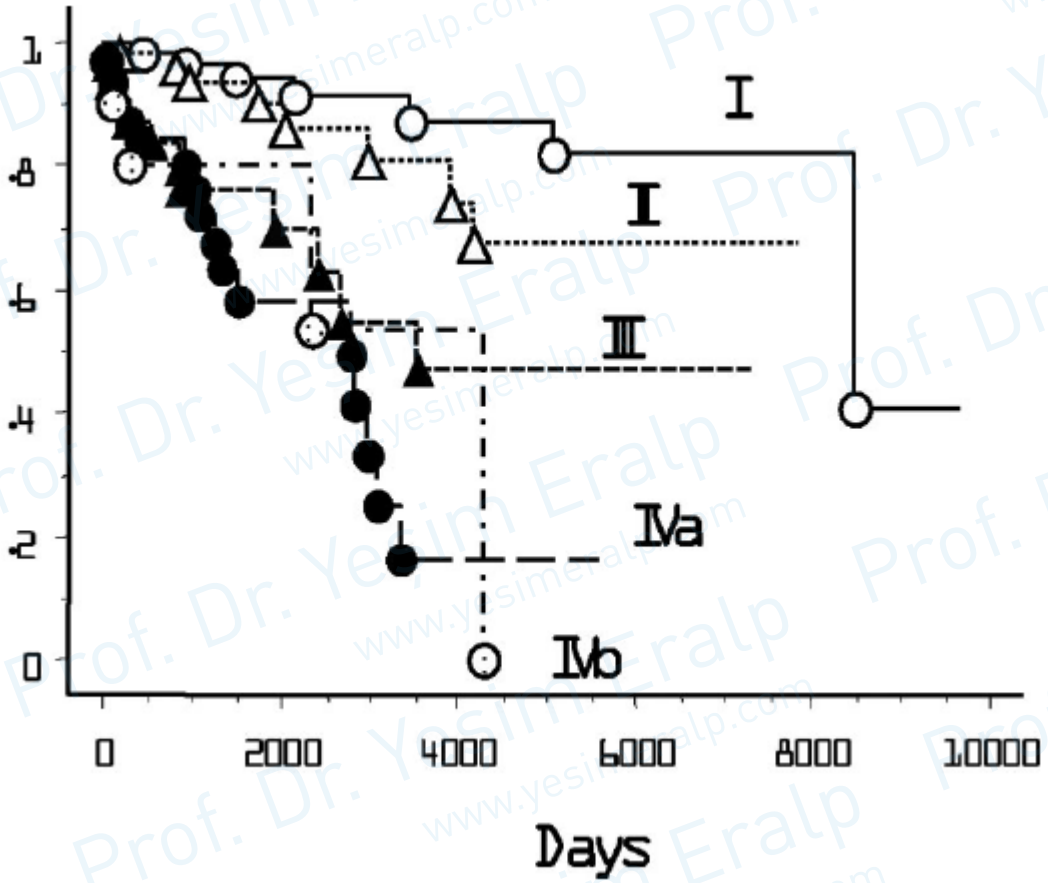
Evre 1 timoma

Altın standart:

komplet rezeksiyon

F. Venuta et al. / European Journal of Cardio-thoracic Surgery 37 (2010)

Masaoka Evre & Sağkalım



I vs II	p:0.11
I vs III	p:0.0001
I vs IV A	p<0.0001
II vs IV B	p:0.0116
III vs IV	p:0.33

Akira Masaoka (*J Thorac Oncol.* 2010;5: S304-

WHO Histolojik Alt-gruplar & Sağkalım

WHO Type	Histologic Description	Incidence[a] (%)	10-Year Survival[b] (%)
A	Medullary thymoma	9	97
AB	Mixed thymoma	24	95
B1	Predominantly cortical thymoma	13	92
B2	Cortical thymoma	24	81
B3	Well-differentiated thymic carcinoma	15	62
C	Thymic carcinoma	15	29

Conrad B. Falkson (*J Thorac Oncol.* 2009;4: 911–919)

Prognostik Kriterler

Evre: Masoka

- I — LOKAL HASTALIK
- IIA
- IIB
- III
- IVA — LOKAL/BÖLGESEL – İLERİ HASTALIK
- IVB — METASTATİK HASTALIK

Histoloji: WHO

- A
- AB — "selim"
- B1
- B2
- B3
- Timik Karsinom — "agresif"

Prognostik Kriterler

Evre: Masoka	Histoloji: WHO
• IIA • IIB • III • IVA	• B1 • B2 • B3 • Timik Karsinom

Multimodal Tedavi

Timik Maliniteler:
Multidisipliner Onkolojik Yaklaşımlar

Adjuvan
- Radyoterapi
- Kemoterapi
- Kemoterapi-Radyoterapi

Neoadjuvan
- Kemoterapi
- Kemoterapi-Radyoterapi

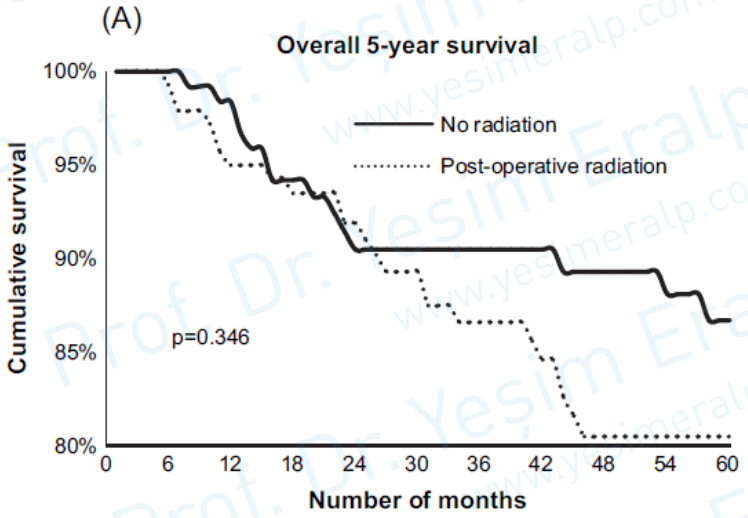
Palyatif
- Kemoterapi
- Kemoterapi-Radyoterapi
- Debulking Cerrahi
- Biyolojik ajanlar
- Hipertermik intraplevral KT

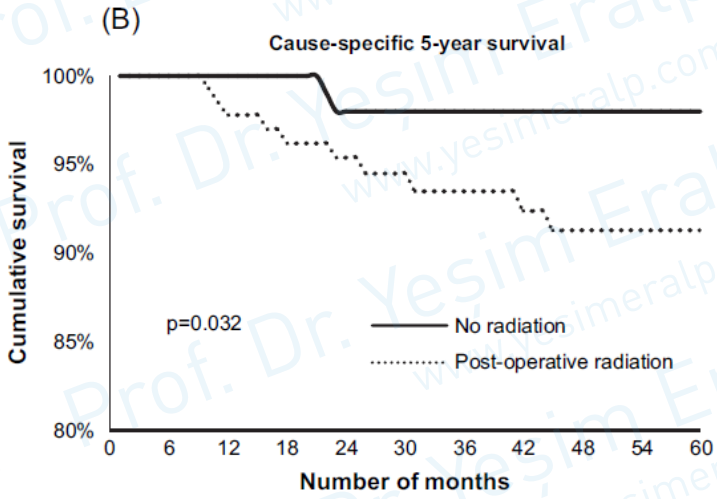
TİMİK NEOPLAZİLERDE RADYOTERAPİNİN ROLÜ

Evre I timoma: postop RT

SEER veritabanı; n: 900 hasta

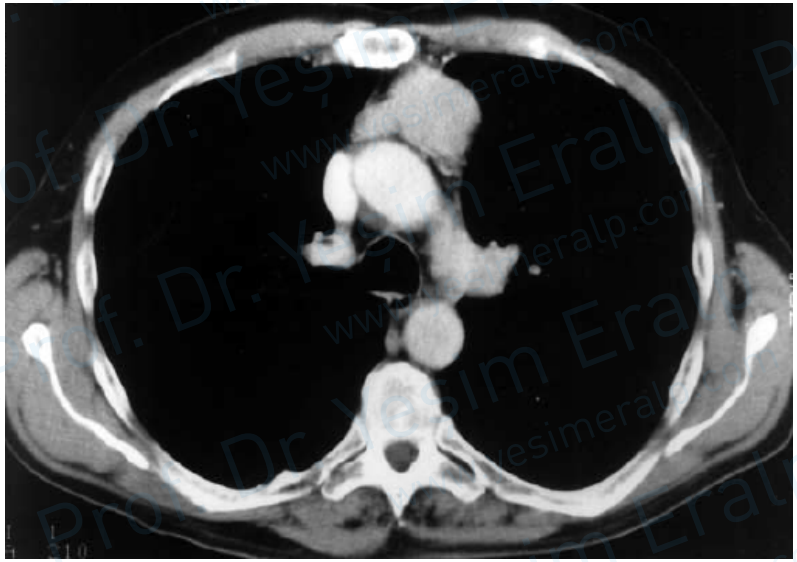
	n	%
Adj RT		
Var	585	65
Yok	316	35
Evre		
Lokalize	275	31
Bölgesel	626	69
Histoloji		
A/AB	105	12
B1-B3	167	19
Timik karsinom	76	8
Timoma, NOS	553	61

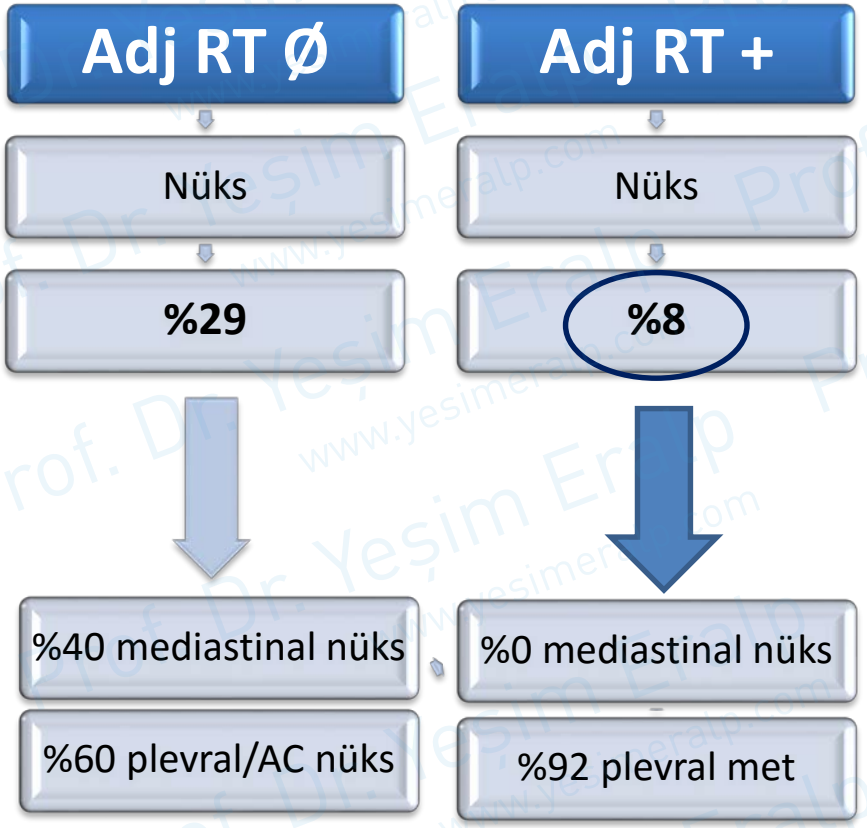




JEFFREY A. FORQUER Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 2, pp. 440–445, 2010

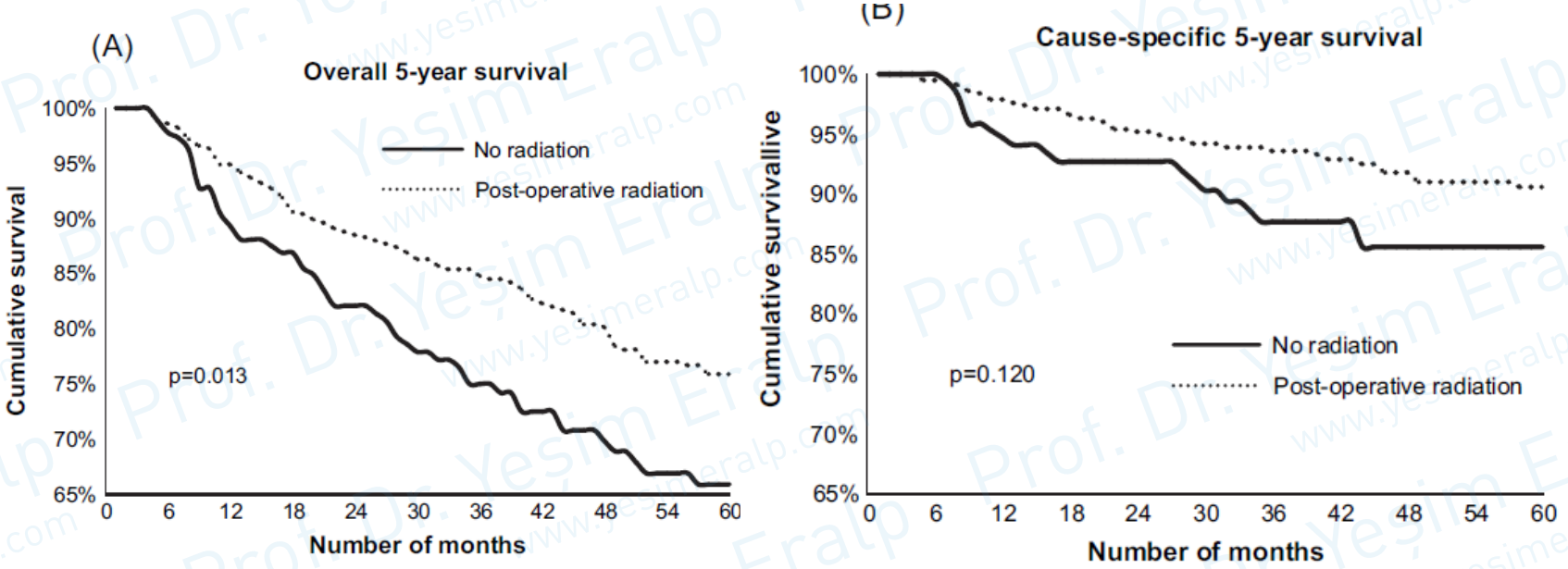
Evre II Timoma





Haniuda M, Ann Surg 224 (1996)
Monden Y, Ann Thorac Surg 39 (1985)
F. Venuta et al. / European Journal of Cardio-thoracic Surgery 37 (2010)

Evre II & III TİMOMA: Adjuvan RT



JEFFREY A. FORQUER. Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 2, pp. 440–445, 2010

Evre II TİMOMA: Radyoterapi

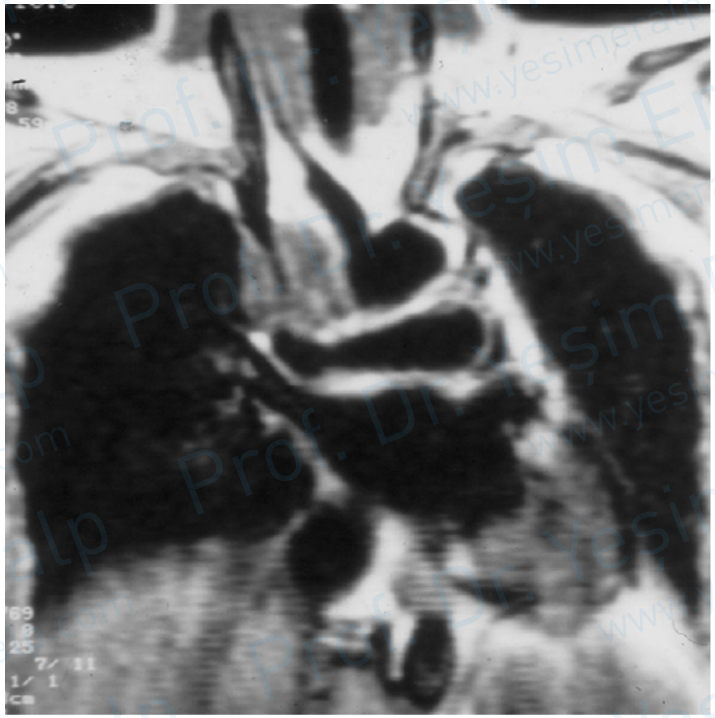
- Yeni serilerde sağkalım farkı yok; 10 yıla kadar %10 nüks olabilir
  - Heterojen hasta grupları
  - Retrospektif değerlendirme
    - RT grubunda daha fazla B3 ve IIB hasta mevcut
  - Kısa takip süreleri

Mangi A, Ann Thorac Surg 2002;74
Singhal S, Ann Thorac Surg 2003;76

- RT önerilen evre II hastalar:
  - IIB
    - Kapsül dışı mediastinal yağ dokusuna makroskopik taşan
    - Perikard veya plevraya yapışık
  - WHO B2-3

Berman A, Cancer 2011;117
Rena O, Eur J Cardiothoracic Surg 2007; 31

Evre III TİMOMA



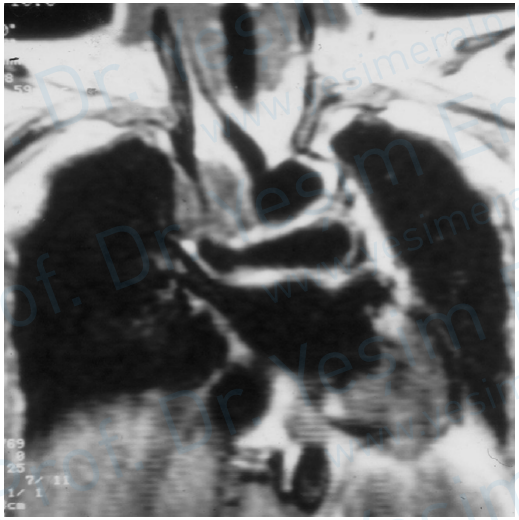
- Mediastinal plevra
- Perikard
- AC
- Büyük damar

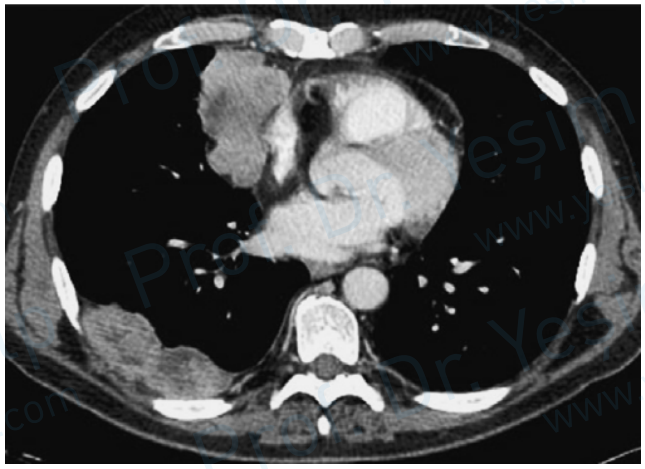
- Komplet rezektabilite: %50 (%0-89)
- 10 yıl sağkalım %35-53

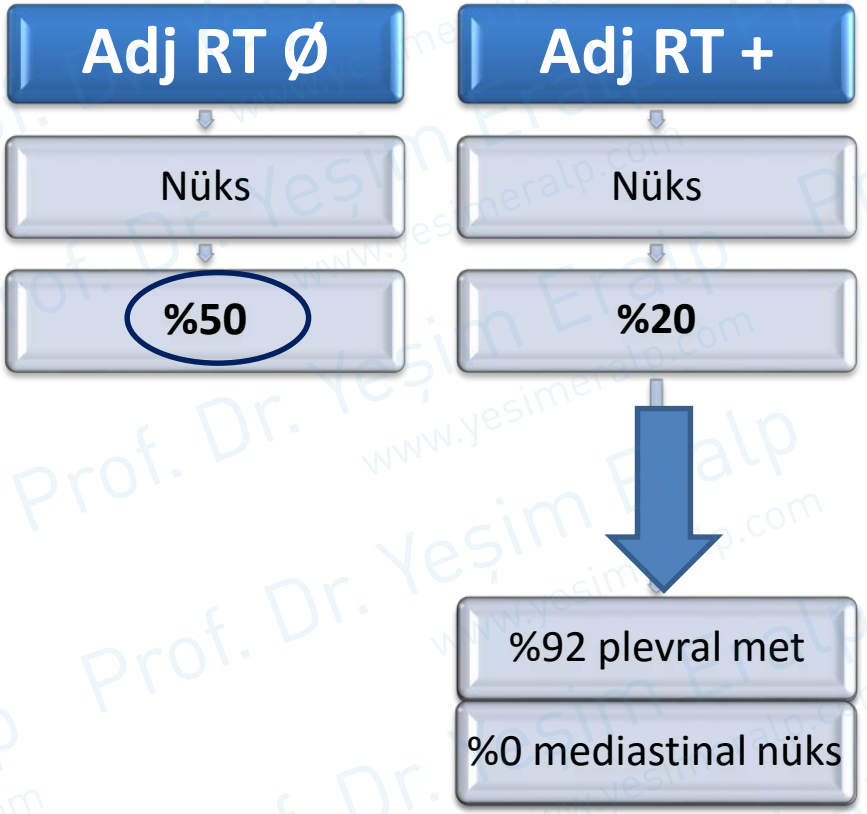
Venuta F, Ann Thorac Surg 76; (2003)
Thomas C, J Clin Oncol 17 (1999)
Ogawa, Cancer 94 (2002)

F. Venuta et al. / European Journal of Cardio-thoracic Surgery 37 (2010)

Evre III & IV A TİMOMA







Curran, J Clin Oncol 6 (1988)
Urgesi, Radiother Oncol 19 (1990)
Ogawa, Cancer 94 (2002)

F. Venuta et al. / European Journal of Cardio-thoracic Surgery 37 (2010)

TİMİK NEOPLAZİLERDE MULTİDİSİPLİNER TEDAVİLER

Timik Neoplazilerde Sistemik Tedavi

Evre: Masoka	Histoloji: WHO
• IIA • IIB • III • IVA	• B1 • B2 • B3 • Timik Karsinom

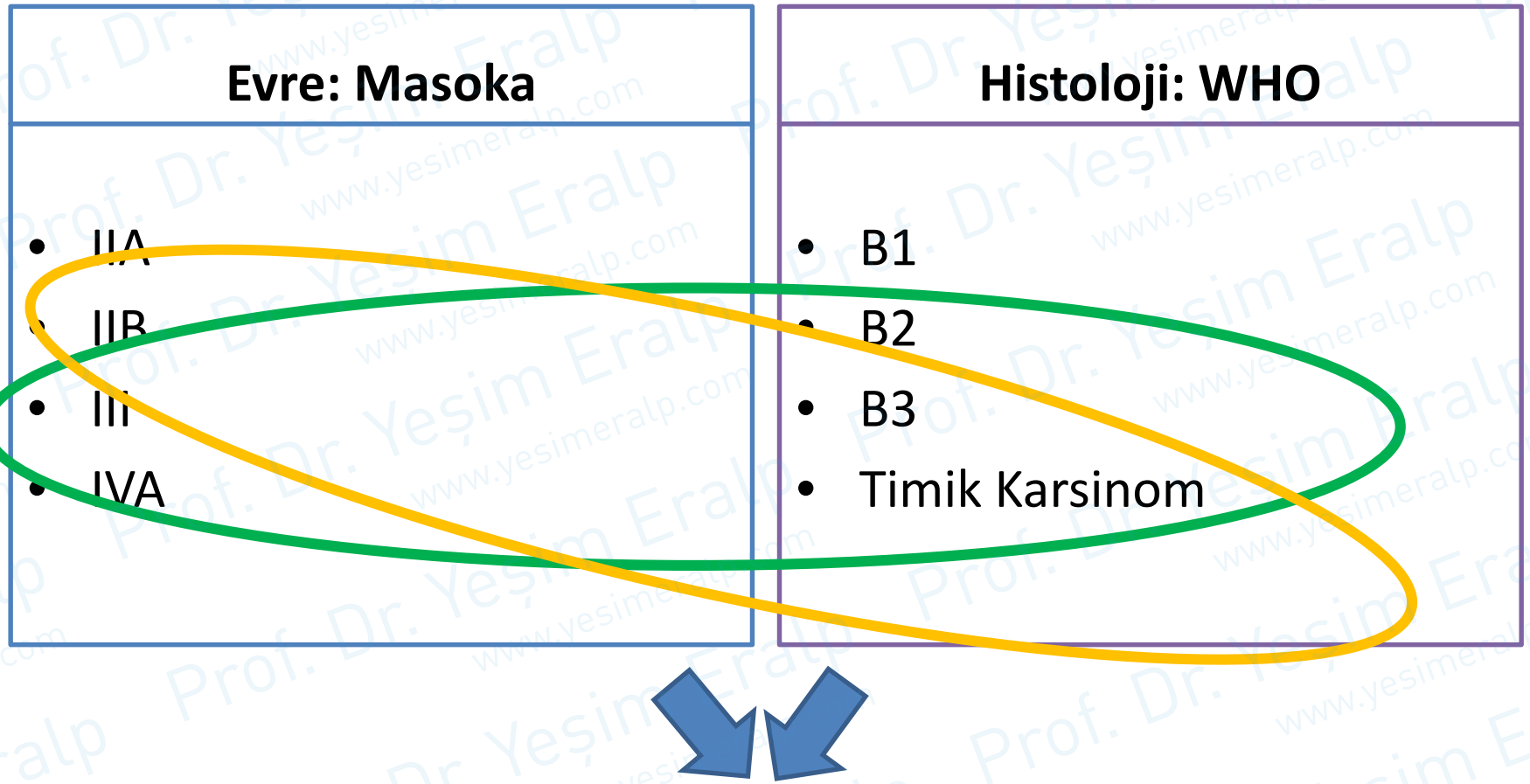
Multimodal Tedavi

Timik Neoplazilerde Sistemik Tedavi

Evre: Masoka	Histoloji: WHO
• IIA • IIB • III • IVA	• B1 • B2 • B3 • Timik Karsinom

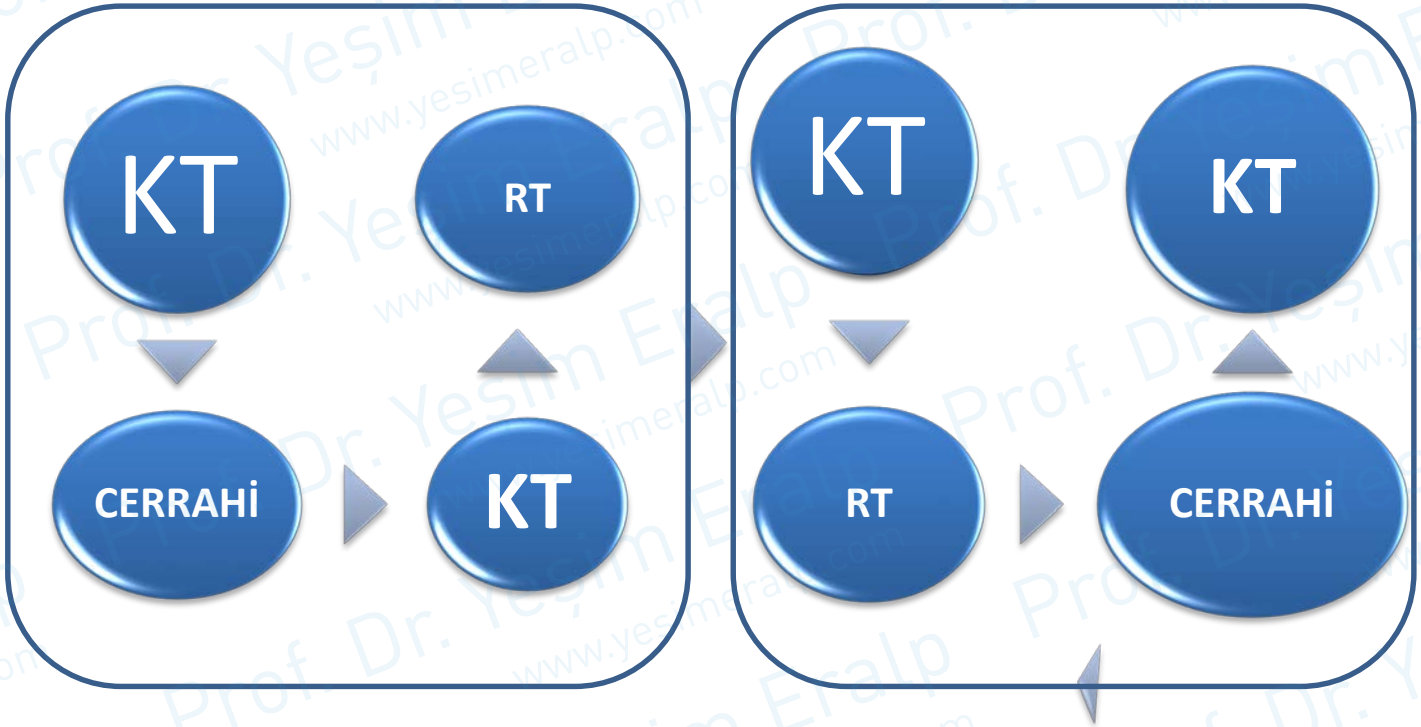
Multimodal Tedavi

Timik Neoplazilerde Sistemik Tedavi



Evre III & IV A Timoma & Multimodal Tedavi Stratejileri:

Sistemik Tedavinin Rolü

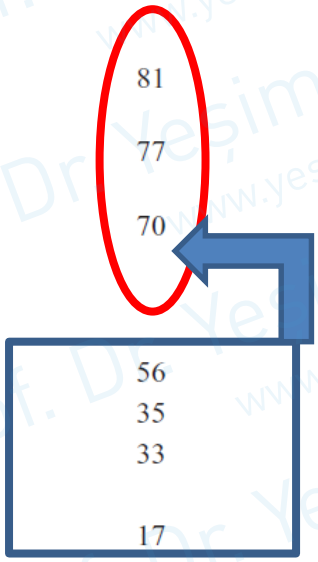


Evre III & IV A Timoma & Multimodal Tedavi Stratejileri: Sistemik Tedavinin Rolü

- Artmış yanıt oranı & R0 rezektabilitenin sağlanması
- Sistemik kontrol
  - Plevral nükslerin kontrolü

Timik Neoplazilerde Sistemik Tedavi:
Evre III-IV Hastalık

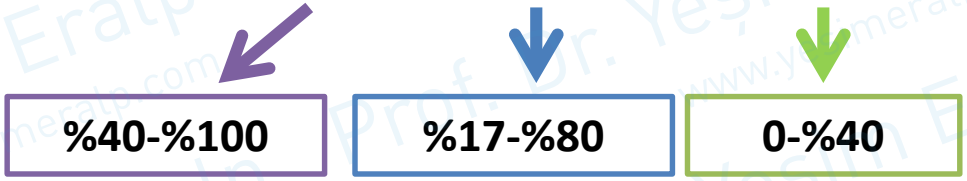
Author	No. of Patients	Chemotherapy Regimen	Response Rate, %	Median Survival (mo)
Platinum-based chemotherapy with anthracycline				
Berruti et al.[10]	16	Cisplatin, doxorubicin, vincristine, cyclophosphamide (ADOC)[a]	81	48
Kim et al.[11]	22	Cyclophosphamide, doxorubicin, cisplatin, predinisone (CAP+P)[a]	77	95% at 5 yr (median not reached)
Loehrer et al.[12]	23	Cyclophosphamide, doxorubicin, cisplatin, (CAP)[a]	70	93
Platinum-based chemotherapy without anthracycline				
Giaccone et al.[13]	16	Cisplatin, etoposide	56	51.6
Loehrer et al.[14]	28 (8 TC)	Cisplatin, ifosfamide, etoposide (VIP)	35	31.6
Lemma et al.[15]	24	Carboplatin, paclitaxel	33	>60
Nonplatinum chemotherapy				
Loehrer et al.[16]	27 (11 TC)	Pemetrexed alone	17	NR



Nicole G. Chau J Thorac Oncol. 2010;5: S313

İndüksiyon Kemoterapisi & Rezektabilite

Author		No. of Patients	Chemotherapy	Response (CR + PR)	Complete Resection	Pathologic Complete Response
Bretti et al.[20]	2004	25	Etoposide, cisplatin or doxorubicin, cisplatin, vincristine, cyclophosphamide	18/25	11/25	2/25
Lucchi et al.[21]	2005	25	Cisplatin, epirubicin, etoposide		20	
Venuta et al.[22]	2003	15	Cisplatin, epirubicin, etoposide	10/15		1/15
Berruti et al.[11]	1993	6	Doxorubicin, cisplatin, vincristine, cyclophosphamide	5/6	1/6	0
Jacot et al.[23]	2005	5	Cisplatin, doxorubicin, cyclophosphamide	4/5	1/5	
Macchiarini et al.[13]	1991	7	Cisplatin, epirubicin, etoposide	7/7	4/7	
Kim et al.[12]	2004	22	Cisplatin, doxorubicin, cyclophosphamide, prednisone	17/22	16/21	6/16[a]
Rea et al.[24]	1993	16	Doxorubicin, cisplatin, vincristine, cyclophosphamide	16/16	11	5/16
Wright et al.[15]	2008	10	Etoposide, cisplatin, radiation therapy	4/10	8/10	4/10[b]
Kunitoh et al.[14]	2010	21	Cisplatin, vincristine, doxorubicin, etoposide	13/21	9/21	3/21



Gregory J. Riely, J Thorac Oncol. 2010;5: S323

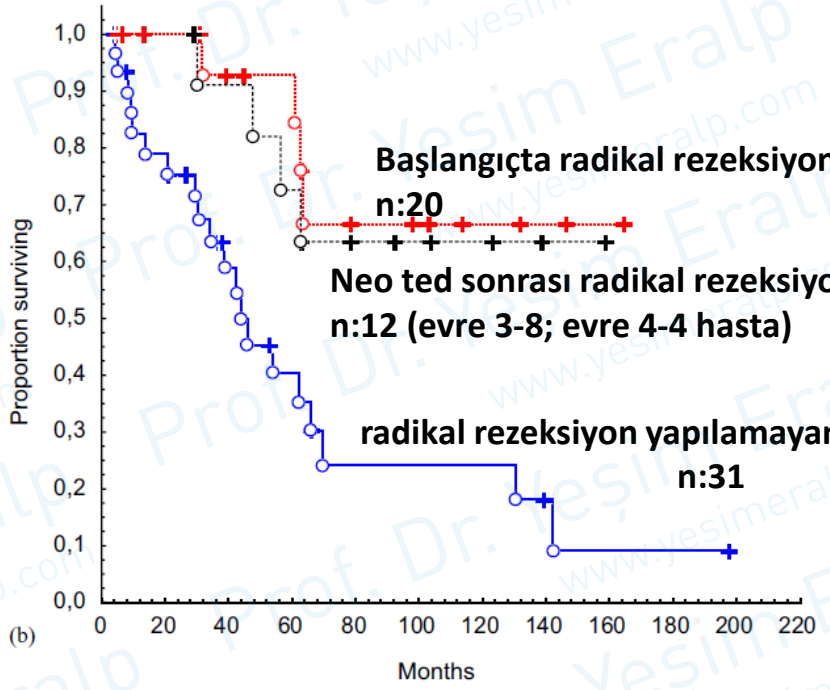
Rezeke Edilemeyen Hastalık: Multidisipliner Tedavi ile Sağkalım

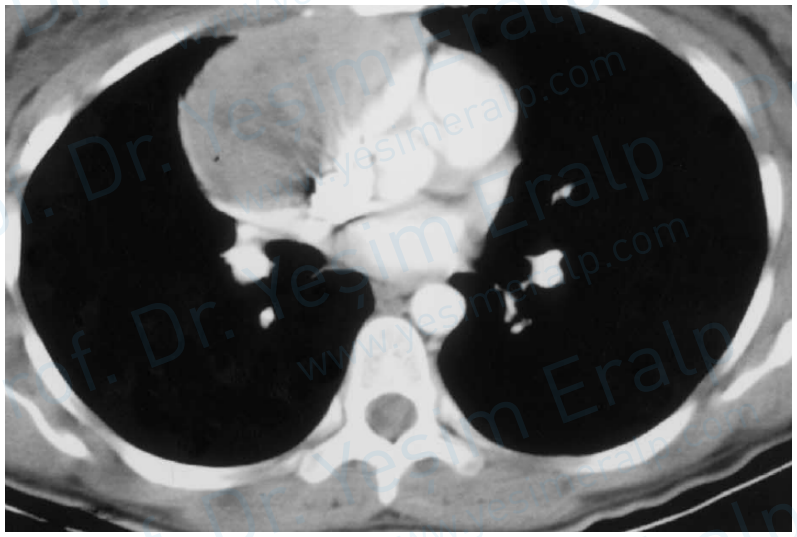
Yazar	N	KT	Komplet rezeksiyon (%)	5 yıl sağkalım (%)
Bretti, ‘04	25	CAPP/VP	44	85#
Lucchi, ‘06	30	PEV	80	86 /76*
Venuta,’03	15	PEV	91	85/56**
Berruti, ‘93	6	CAP-O	17	NA
Jacot, ‘05	5	PEV	20	NA
Macchiarini, ‘93	7	CAP-P	57	NA
Kim,’04	22	CAP-O	76	95
Rea, ‘93	16	CAP-P	69	70^
Wright, ‘08	10	VP	80	69
Kunitoh,’10	21	CAV-O	43	85

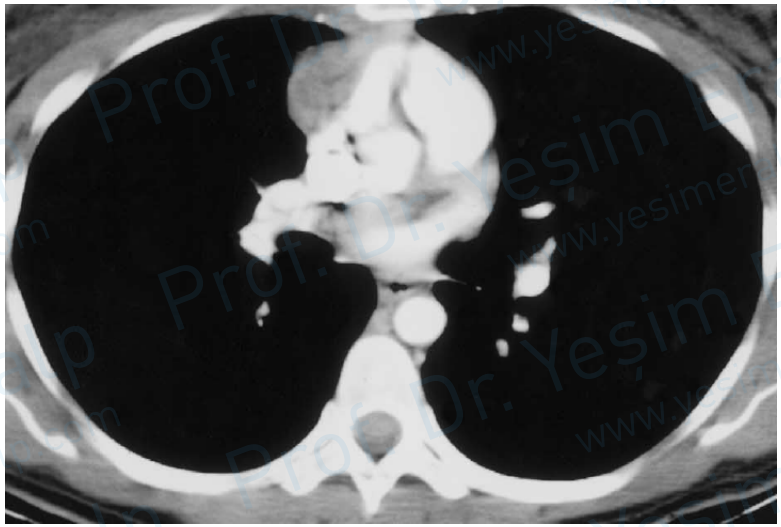
#:st 3 vs 4a: 142 vs 46 mo; *: 10 yr; st ¾; **: 10 yr, B2/B3; ^:3 yr

Multidisipliner Tedavi

63 hasta;
evre III-n: 43; IV A-n:20







Bretti Lung Cancer (2004) 44, 69-
Kim Lung Cancer (2004) 44, 369

Cerrahi sonrası konsolidasyon KT gerekir mi?

Nüks Paternleri

Adjuvan RT

- N:84; %30 göğüs dışı nüks
  Park, '94
- %27 uzak nüks
  Rea, '93
- N:63; %25 göğüs dışı nüks,
  %44 göğüs içi nüks
  Bretti, '04
- 5 yıl OS: %53
  Loehrer, '97

Adjuvan RT + Konsolidasyon KT

- N:14; 10 hasta nüks
  %70 lokal-dışı yayılım;
  radikal nüks tedavisi
  10 yıl OS evre III: %100
  10 yıl OS evre IV A: %89
  Yokoi, '07
- 5 yıl OS: %92 **Kim, '04**

ORIGINAL PAPER

Association of clinical and pathological variables with survival in thymoma

Adnan Aydiner · Alper Toker · Fatma Sen · Ercan Bicakci · Esra Kaytan Saglam · Suat Erus · Yesim Eralp · Faruk Tas · Ethem Nezih Oral · Erkan Topuz · Sukru Dilege

İstanbul Üniversitesi Torasik Onkoloji Grubu
TİMİK NEOPLAZİLER & MULTİMODAL TEDAVİ

	N	%
Masoaka		
2	3	15.8
3	4	21.1
4	12	63.2
WHO histoloji		
A	2	10.5
B1	5	26.3
B2	4	21.1
B3	8	42.1
Cins		
K	9	47.4
E	10	52.6
Myasteni		
Var	3	15.8
Yok	16	84.2

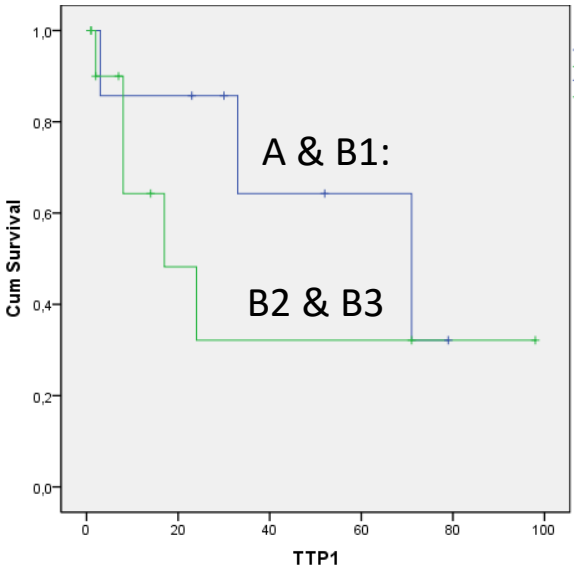
- 1995-2010: 140 hasta
  - C: 35 (%25);
  - C+adjuvan CT/RT:86 (%62)
- Başta inop olan 19 hasta
  - multimodal tedavi adayı
  - Neoadjuvan KT: 1-6 kür (ort:3)
- Yaş: 50 (16-80)
- Medyan takip: 20 ay (1-98)
- KT yanıt:
  - PR: 6 (%31.6)
  - Stabil: 7 (%36.8)
  - Progresyon :5 (%26.3)
- Cerrahi
  - R0: 11 (%57.9)
  - R2:2 (%10.5)
  - Yapılamayan: 5 (%26.3)

Sen F; Med Oncol (2012) 29:2221

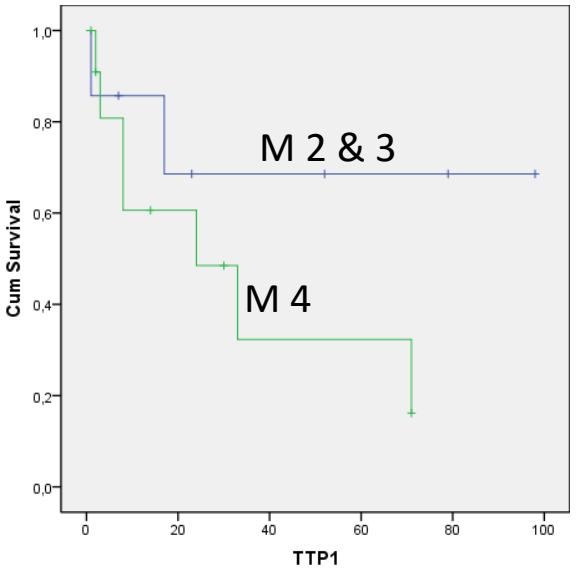
ITF Timik Maliniteler:
Multimodal Tedavi & Progresyonsuz Sağkalım

- **Medyan takip: 16 ay (1-100 ay)**
- **8 hastada (%42.1) progresyon var**
  - **5 yıl PFS: %46.2 ±13.7; medyan 33 ay**
  - **5 yıl GS: %60.8 ±11.7**

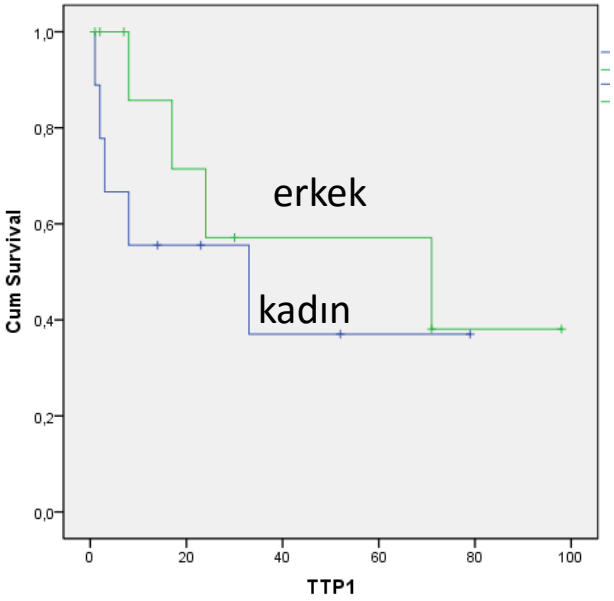
- **Son durum:**
  - **NED: 6 (%31.5)**
  - **AWD:5 (%26.3)**
  - **EX: 8 (%42.1)**
    - **3: post-op**
    - **1: KT sonrası pulm emboli**
    - **4: hastalık**



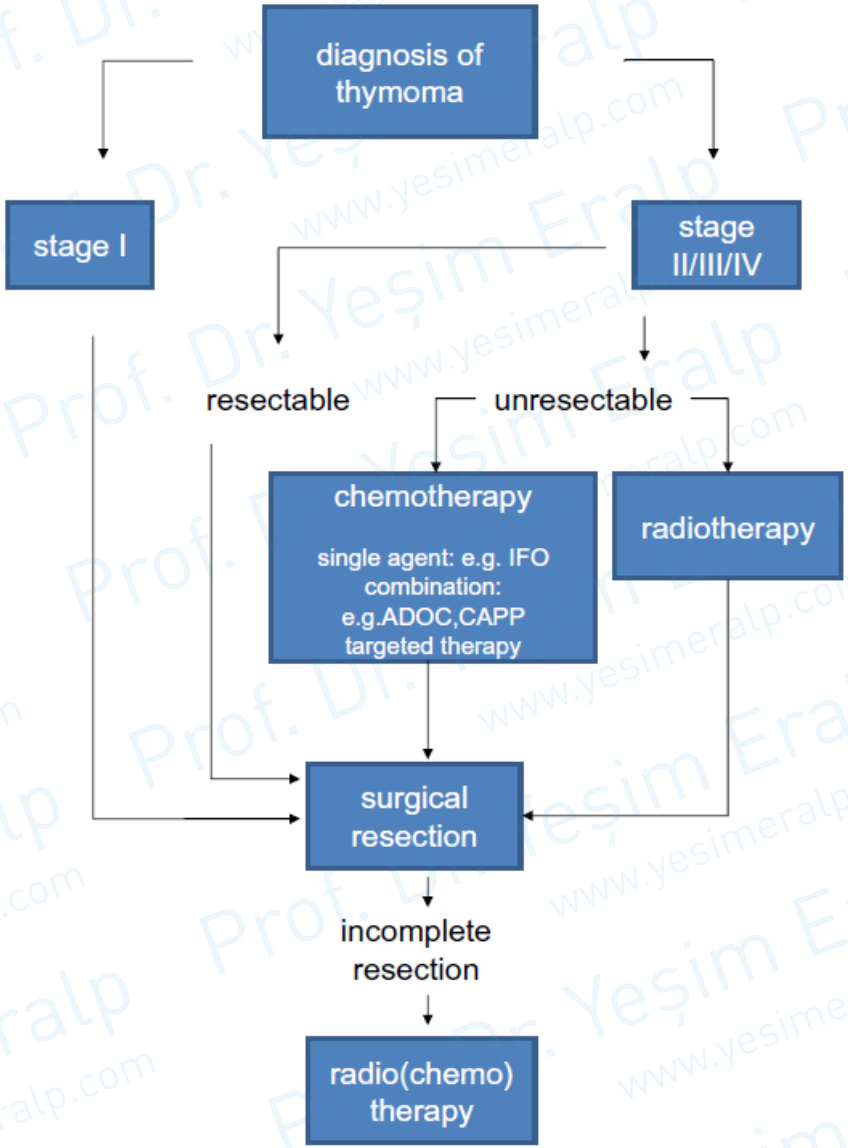
A & B1: 71 ay
B2 & B3: 17 ay
NS

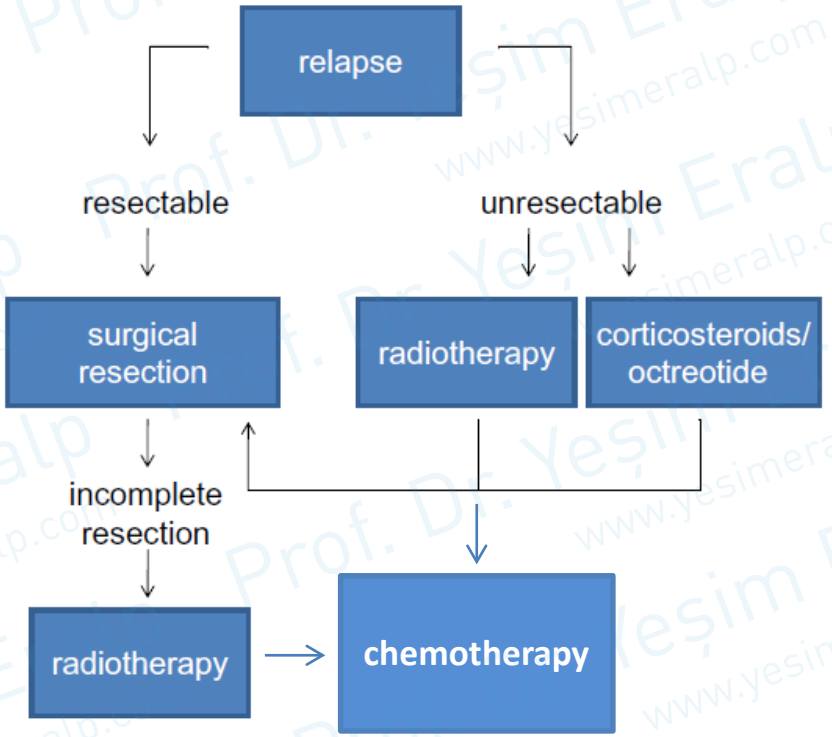


M 2 & 3: 70 ay
M 4: 33 ay
NS



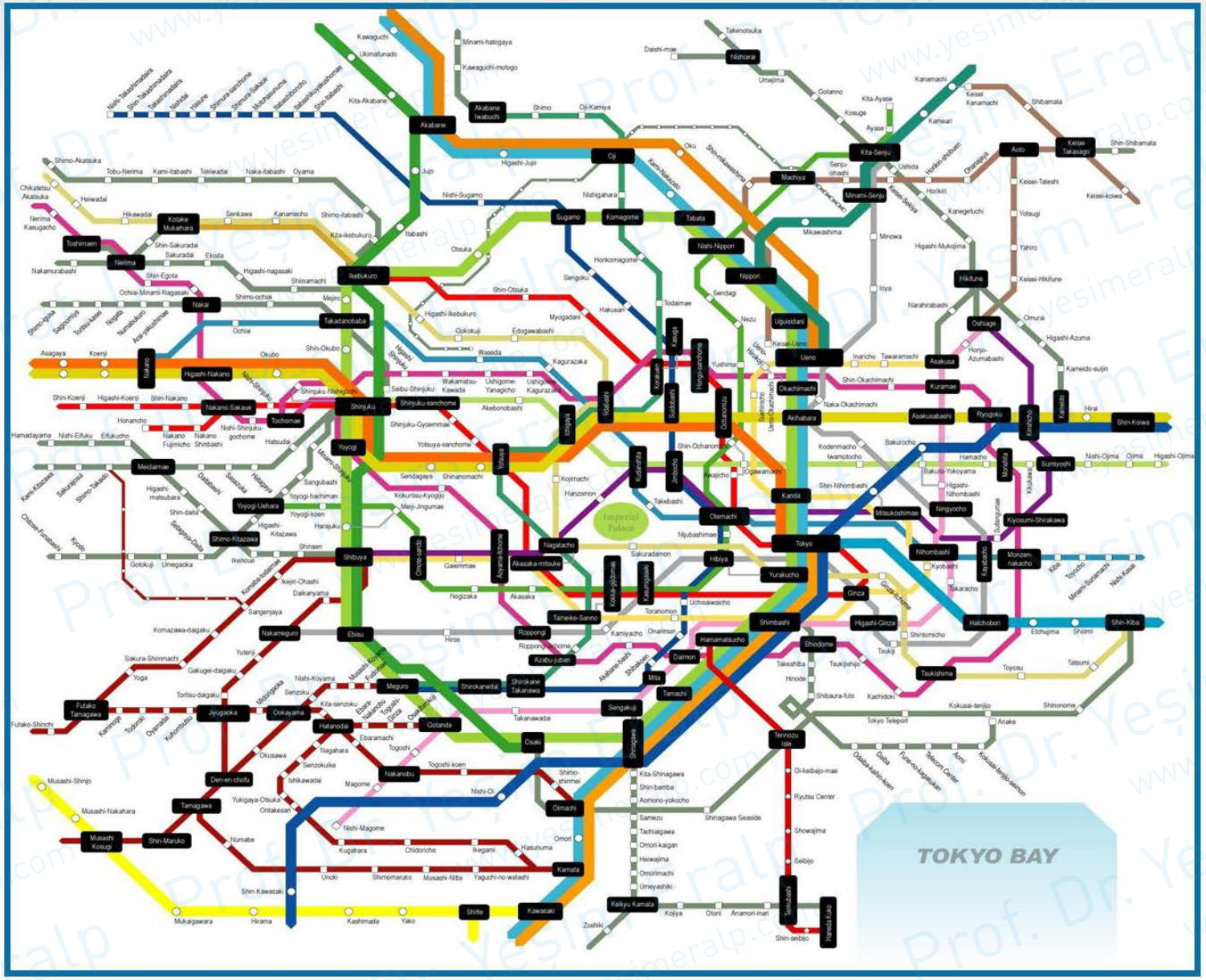
erkek: 71 ay
kadın: 33 ay
NS

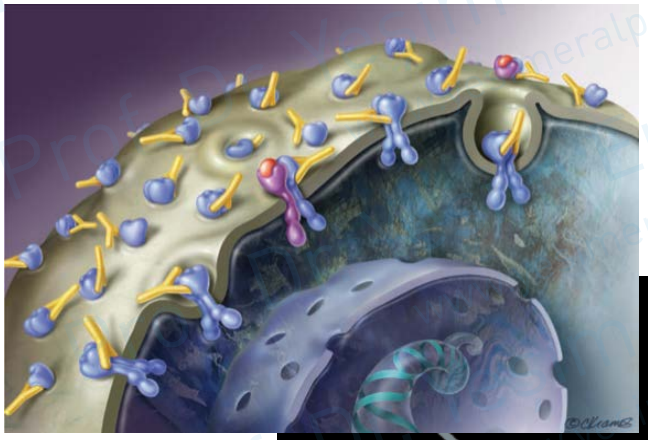

diagnosis of thymoma
stage I
stage II/III/IV
resectable
unresectable
chemotherapy
single agent: e.g. IFO
combination:
e.g.ADOC,CAPP
targeted therapy
radiotherapy
surgical resection
incomplete resection
radio(chemo) therapy

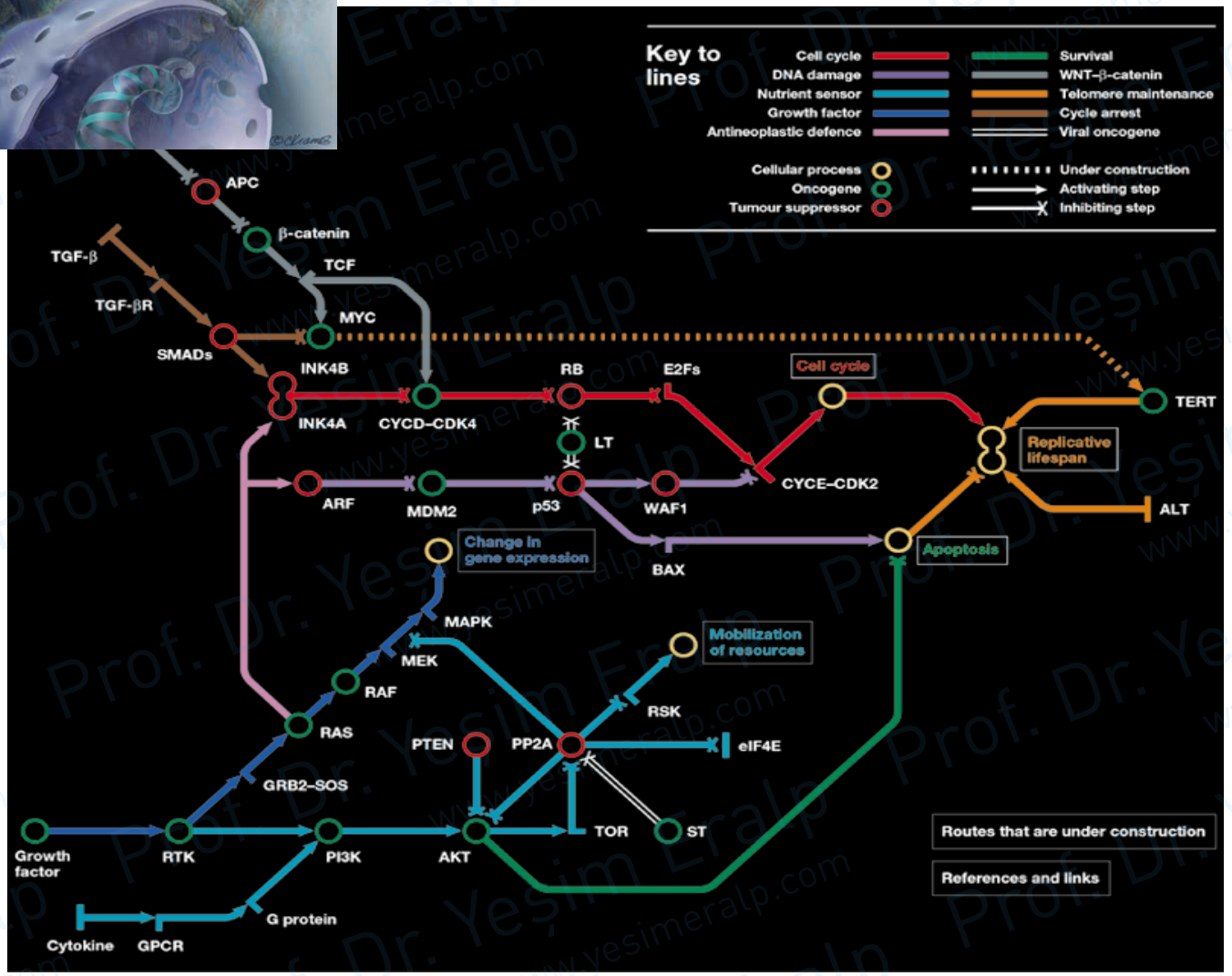

relapse
resectable
unresectable
surgical resection
radiotherapy
corticosteroids/ octreotide
incomplete resection
radiotherapy
chemotherapy

GELECEK BEKLENTİLER

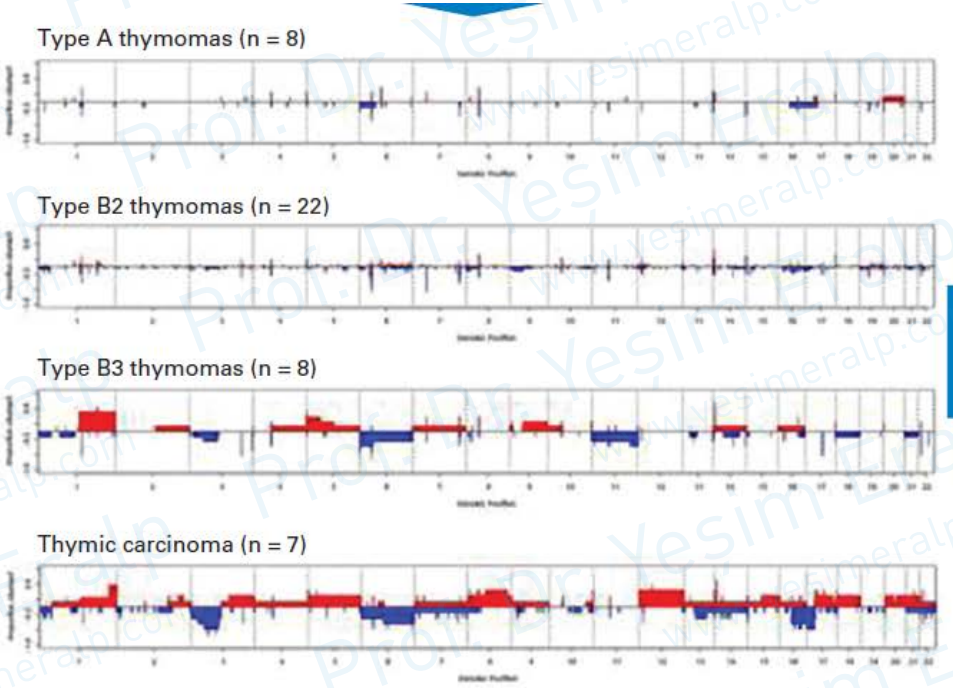
Tokyo Subway Map: Analogy of Biochemical Pathways

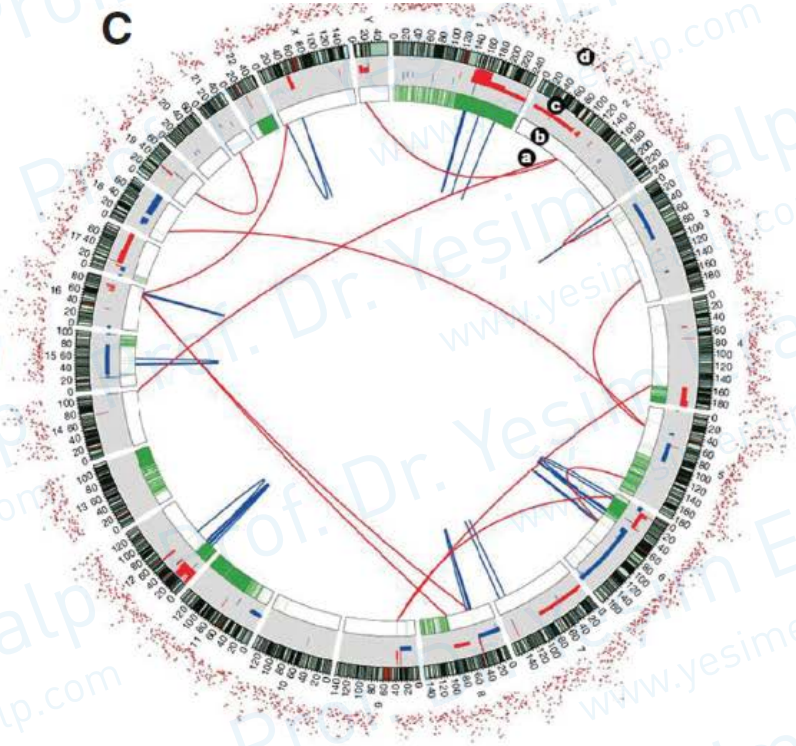





Key to lines
Cell cycle
DNA damage
Nutrient sensor
Growth factor
Antineoplastic defence
Survival
WNT–β–catenin
Telomere maintenance
Cycle arrest
Viral oncogene
Cellular process
Oncogene
Tumour suppressor
Under construction
Activating step
Inhibiting step
APC
β-catenin
TCF
MYC
TGF-β
TGF-βR
SMADs
INK4B
INK4A
CYCD–CDK4
RB
E2Fs
LT
Cell cycle
TERT
Replicative lifespan
ALT
CYCE–CDK2
ARF
MDM2
p53
WAF1
BAX
Change in gene expression
Apoptosis
MAPK
MEK
RAF
RAS
GRB2–SOS
Mobilization of resources
RSK
PTEN
PP2A
eIF4E
TOR
ST
Growth factor
RTK
PI3K
AKT
G protein
Cytokine
GPCR
Routes that are under construction
References and links

Timoma & Genomik Karakterizasyon





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Timik Maliniteler & Tedavi Hedefleri

Oncogene/Molecular Change	Thymoma (%)	Thymic Carcinoma (%)
EGFR		
Gene amplification (FISH)	20	25
Overexpression (IHC)	23	67-100
HER2		
Overexpression (IHC)	6	53
c-KIT (CD117)		
Overexpression (IHC)	< 5	73-86
BCL2		
Overexpression (IHC)	14	100
Tumor suppressor genes		
TP53		
LOH	0	38
Mutation	0	11-30
Overexpression (IHC)	12-100	80-100
P16INK4A		
LOH	0	25
Loss of expression	40-50	70

Multimodal Tedavide Yeni Arayışlar: Hedefe Yönelik Ajanların Entegrasyonu

- Octreotid
- VEGF-
  - Bevacizumab
  - Sunitinib & sorafenib
- IGFR-1-
  - cixutimumab

EGFR-
  Cetuximab
  Erlotinib & gefitinib
- C-kit
  - imatinib
- HDAC
  - belinostat

Reference	Drug	No. of Patients	Thymic Thymoma	Thymic Carcinoma	RR	SD	PD
Kurup et al[63]	Gefitinib	26	19	7	1	14	—
Bedano et al[70]	Erlotinib + bevacizumab	18	11	7	0	11	7
Giaccone et al[71]	Imatinib	7	2	5	0	2	5
Salter et al[72]	Imatinib	11	0	11	0	3	4
Giaccone et al[73]	Belinostat	41	25	16	2	25	13

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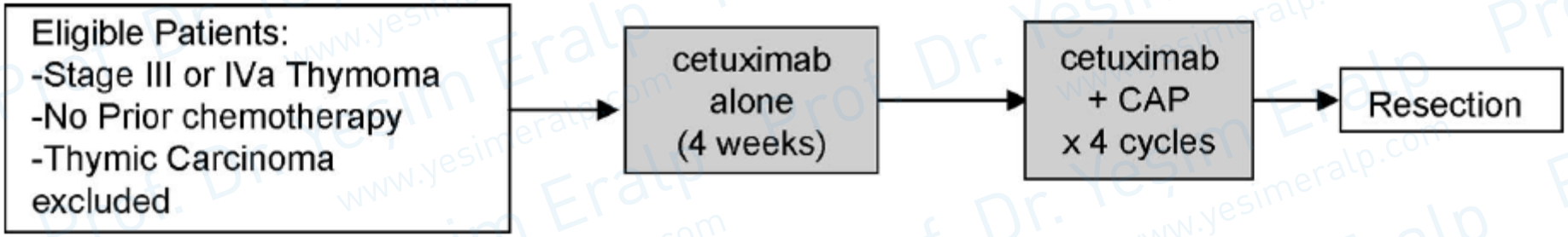
Multimodal Tedavide Yeni Arayışlar: Hedefe Yönelik Ajanların Entegrasyonu



ClinicalTrials.gov

A service of the U.S. National Institutes of Health

MK-3475 in Patients With Thymic Carcinoma

Drug: MK-3475

Administration of 200 mg MK-3475 once every 3 weeks

Other Names:

- Keytruda
- Pembrolizumab