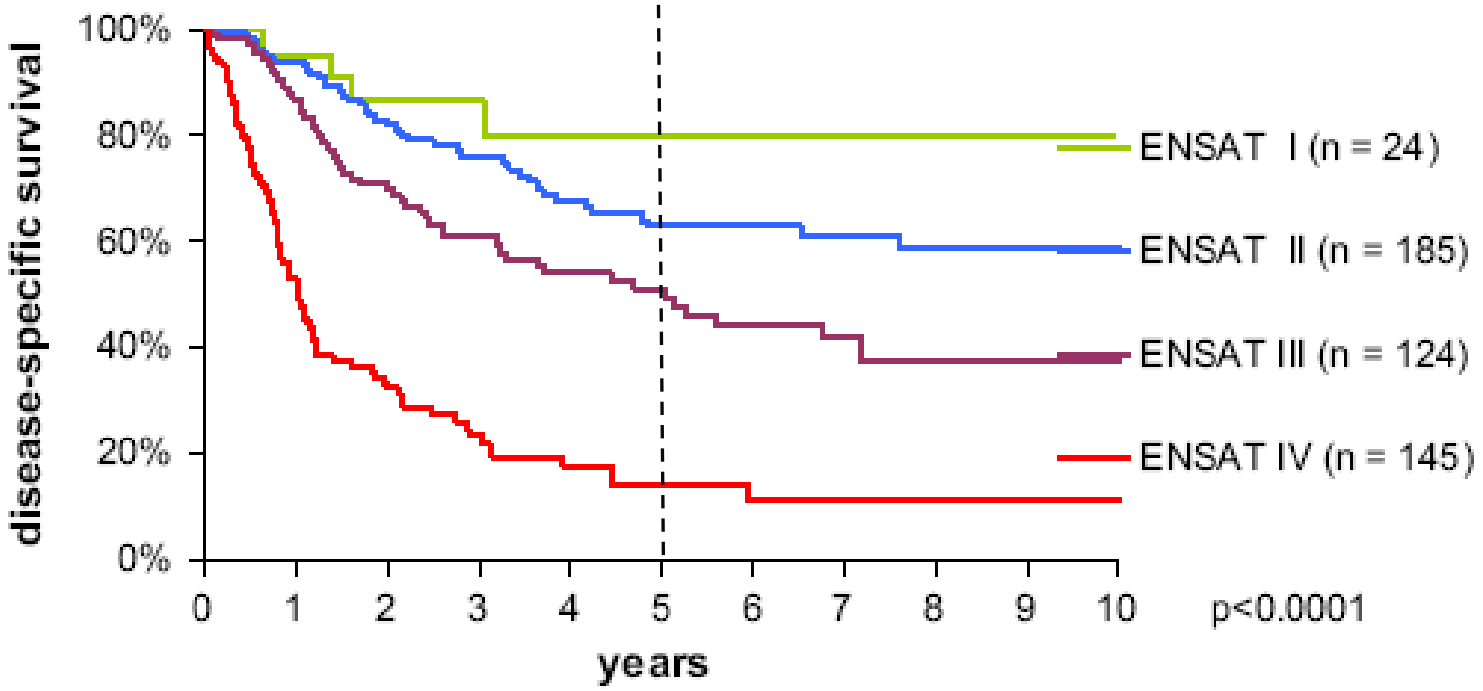
Twenty years experience with mitotane as adjuvant therapy for adrenocortical carcinoma

Gabriel Dickstein,
Carmela Shechner
Jacob Bejar
Bnai Zion Medical Center

Adrenocortical carcinoma - prevalence

- Textbooks – 1:1000000 per year
- France (population 60600000) – 202 cases in 40 years – 5 cases per year
- Italy (population 58000000) – 47 cases in 15 years – 3 cases per year.
- Germany registry (population 82000000) – 478 cases – 6 per million.
- USA (population 306000000) – 290 cases in 1994-2000 – 41 cases per year.

Acc – disease free survival



5. Disease-specific survival according tumour stage (ENSAT classification: see Table 2); data derived from the German stry, August 2008.

Outcome and Prognostic Factors (Paris, France, 2003)

202 patients in 40 years:

Glucocorticoid hypersecretion – 113.

Androgen hypersecretion – 82.

Silent – 48.

Survival:

1 year – 71%.

2 years – 57%.

5 years – 37%.

8 years – 31%.

Sloan-Kettering (Arch Surg 1999)

- Total number – 46 patients with curative adrenalectomy.
- Tumor size – 2.5 – 27 cms (median 15).
- 5 y survival : overall - 36%.
- Larger than 12 cms – 22%.
- No metastatic patients included.

Shumacher, Cleveland Clinic (1991)

- First to introduce adjuvant mitotane, 1- 4grm after surgery:
- 11 patients:

  6 disease free – median time 12.5 years

  range – 5 to 18 years

  5 died within 2 years after mitotane discontinued, 3-17 years of treatment.

  Therefore, long term treatment is crucial.

Kasperlik – Zaluska (Cancer 1995)

- **Five year survival:**

  Surgery only – 2 out of 7 (29%).

  Surgery + Mitotane – 12 out of 26 (46%).

  However:

  Immediate adjuvant mitotane – 10 of 13 (77%).

  Delay of 3-15 months – 2 out of 13 (15%).

Therefore, immediate treatment is crucial.

בשנת 1998 תיארנו ארבעה מקרים קשים של ACC שהגיבו היטב לטיפול במיטוטן לאחר הרחקה מלאה של הגידול

Is There a Role for Low Doses of Mitotane (o,p′-DDD) as Adjuvant Therapy in Adrenocortical Carcinoma?

GABRIEL DICKSTEIN, CARMELA SHECHNER, ELDAD ARAD, LAEL-ANSON BEST, AND OFER NATIV

Division of Endocrinology (G.D., C.S., E.A.) and Department of Urology (O.N.), Bnai Zion Medical Center, Haifa, Israel, and Department of Chest Surgery, Rambam Medical Center (L.-A. B.), Haifa, Israel

ABSTRACT

Four patients suffering from adrenocortical carcinoma were treated with low doses (1.5–2.0 g) of mitotane (o,p′-DDD) for the complete follow-up time following surgery (21–68 months). Treatment with mitotane was started shortly after surgical removal of the tumor (three patients) or the tumor and multiple lung metastasis (one patient). No significant side effects or complications from the medication were noted. Two patients remain disease free after 57 and 21 months on treatment. A third patient died of an unrelated reason (varicose vein bleeding) after 68 months on mitotane without evidence of tumor recurrence or metastasis. In the fourth patient, two lung metastasis were successfully removed after 48 months of follow-up. The patient is doing well and is disease free 6 months later. Though our series is too small to draw final conclusions, we suggest that low doses of mitotane, which are well tolerated, might offer prolonged disease-free survival in adrenocortical carcinoma. To be beneficial treatment has to be started early after surgical removal of the tumor and metastasis, and be continued for long periods of time. (*J Clin Endocrinol Metab* **83:** 3100–3103, 1998)

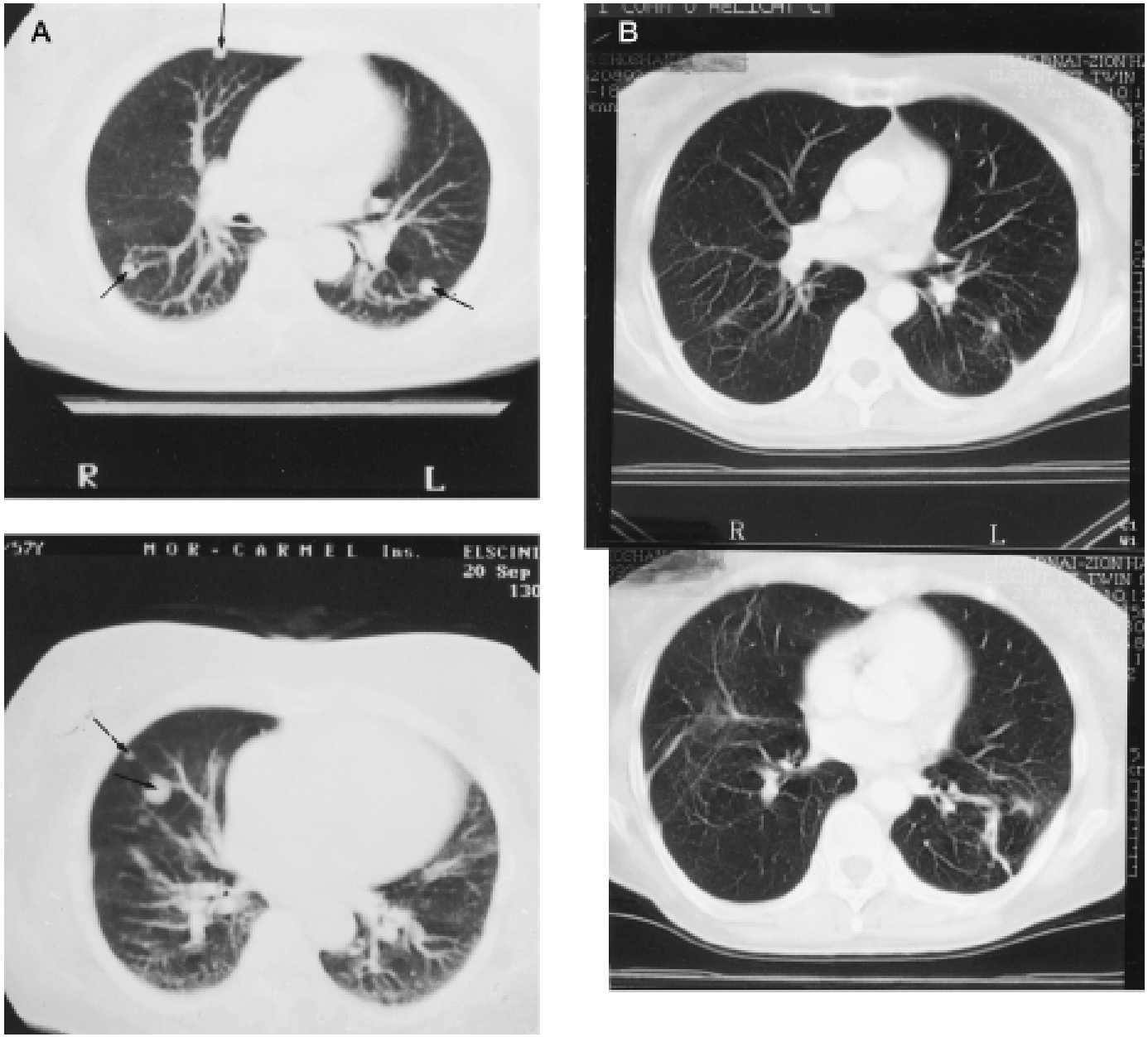


FIG. 1. Chest CT in patient 1 demonstrating multiple metastasis before first surgery (A) and free of metastasis 4.5 yr later (B).

ACC with

12 lung meta

Removed in 2

Surgeries.

No recurrence

In 6.5 years

בת 41, כריתת ACC בשנת 1998

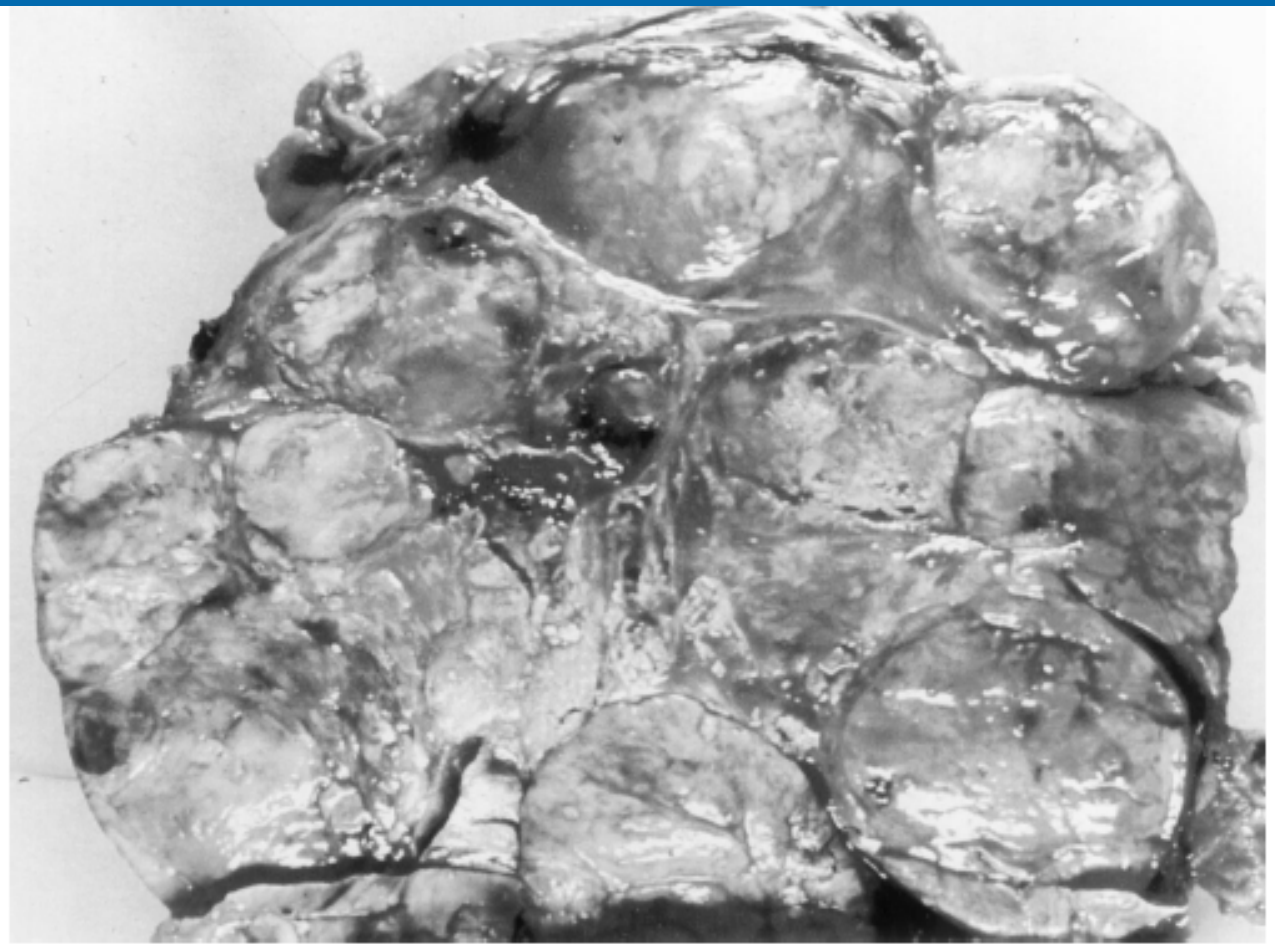


FIG. 3. Macroscopic view of the tumor. The tumor was 17 cm and weighed about 1.5 kg.

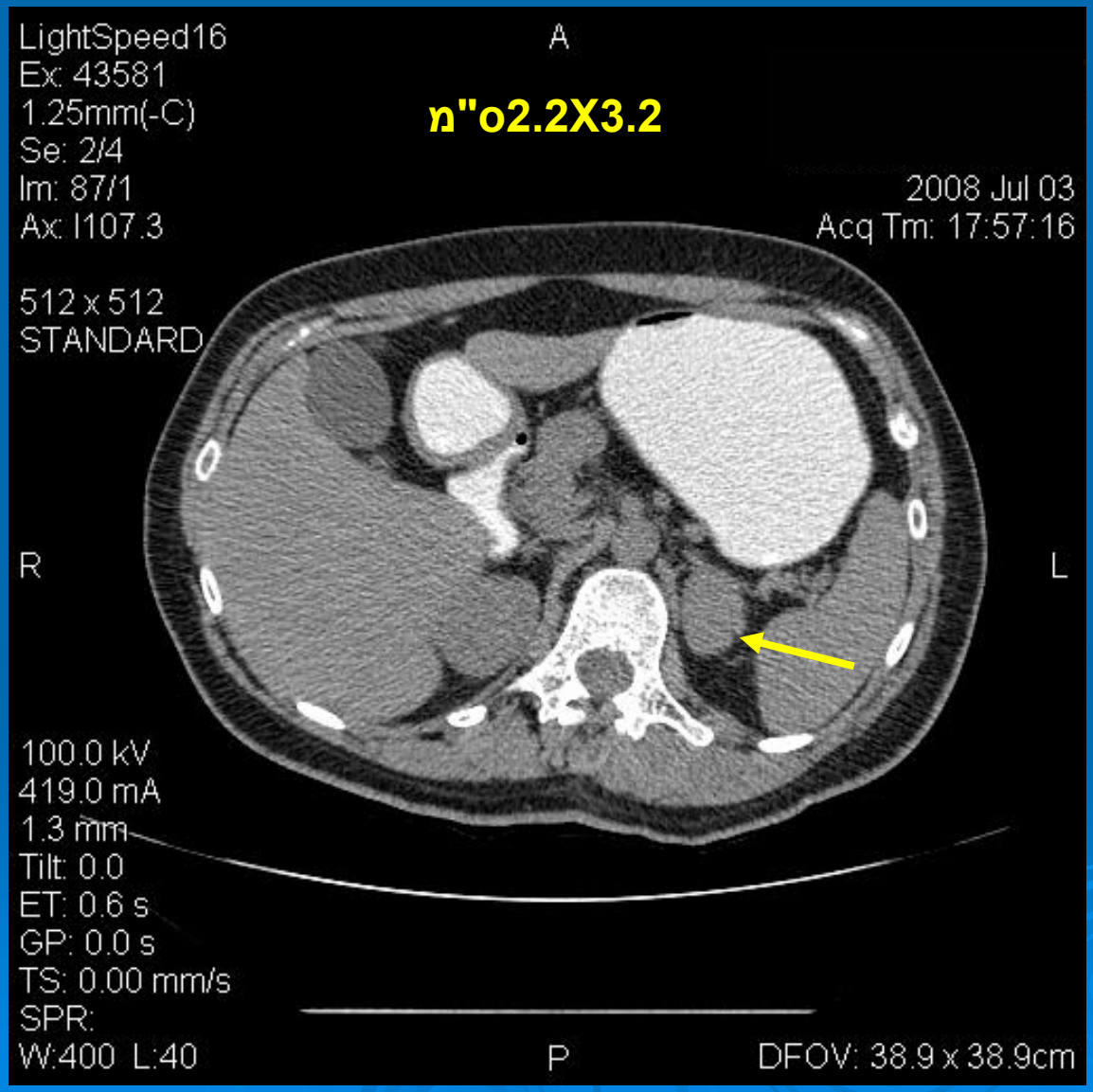
לאחר שנה – גרורה בחוליה L2 – כריתת החוליה. מאז בריאה.

- **לפיכך, כריתה של גרורות מוצדקת והכרחית במידת האפשר בכל שלב של המחלה!**

ACC VS ADENOMA:

WHEN WOULD YOU TREAT POSSIBLE STAGE I ACC WITH MITOTANE?

בת 50, נ +4, בריאה בד"כ
בבדיקת CT, ממצא מיקרי של קשרית באדרנל



ללא קליניקה של CS או פאוכרומוציטומה

ללא יתר לחץ דם

בבירור שבוצע בבית חולים אחר :

SHORT DEX 1MG- CORT 53nmol/l (1.9mcg/dl), 59nmol/l (2.1mcg/dl)

ACTH level – not done.

UFC 71 nmol/24h, 55 nmol/24h (N=42-254)

NORMAL CATECHOLAMINES

בחשד לקושינג תת קליני, נשלחה לניתוח כריתה של הממצא

LAP ADRENALECTOMY LT

היסטולוגיה:

- גוש 4 ס"מ, משקל ?
- גוש ממקור קליפת אדרנל
- הגידול בנוי ברובו מתאים אאוזינופיליים מאורגנים בקוריות ו-nests
- NUCLEAR GRADE III
- פעילות מיטוטית נמוכה
- ללא מיטוזות אטיפיות
- שוליים ניתוחיים חופשיים
- ללא חדירה לורידים
- מוקד אחד של SINUSOIDAL INVASION
- מוקדים רבים של CAPSULAR INVASION
- חדירה לתוך רקמת השומן הסמוכה
- Ki-67 - לא בוצע.

- נקבע שהדירוג ההיסטולוגי הוא 4/9 לפי WEISS, 3/9 לפי AUBERT
- אובחנה כ- GRADE1 Adrenocortical Carcinoma (ACC)

➢ הומלץ על טיפול ב-MITOTANE

החולה הגיעה לחוות דעת נוספת

- נלקחו סליידים לריביזיה

תשובה פתולוגית:

Ki67 positive in less than 1% of tumor cells
Adrenocortical tumor of uncertain malignant potential

- הפרפרטים נשלחו לריביזיה נוספת בחו"ל

William Young

Mayo clinic

Rochester

1. Q: Would you consider this tumor as benign, malignant, or uncertain malignant?
   - A: Uncertain status with regard to malignancy
2. Q: would you consider this case as sufficient for mitotane treatment?
   - A: In a patient like this, I would prefer close observation with imaging q 3 mo x 1 yr, 4 mo x 1 yr, q 6 mo x 2 yr.
   - I don't think there is a "correct" answer to this one.

Massimo Terzolo
University of Torino
Italy

Trying to calculate a Weiss score the outcome is possibly 2-3. (eosynophil cells + capsular invasion + possibly sinusoidal invasion).

If the outcome will be 2, I will not treat with mitotane but do an imaging follow-up, if the outcome is 3 the patient will be a perfect candidate for the “Adiuvo” trial which wants to randomize to mitotane VS observation patients at low-risk of recurrence.

Prof Allolio
Dep. End. Dia.
University of Wuerzburg

The tumor is small, no necrosis and a rather low Ki67.
If a Ro resection was performed we would not give mitotane.
Suggest revision of slides by Prof. Saeger.

Prof Wolfgang Saeger
Institute of pathology of the marienkrankenhaus
Hamburg

It is an adrenal adenoma with partial myelolipomatous Metaplasia. The Ki-67 Index is very low, no clear mitosis, no necrosis, no signs of malignancy.

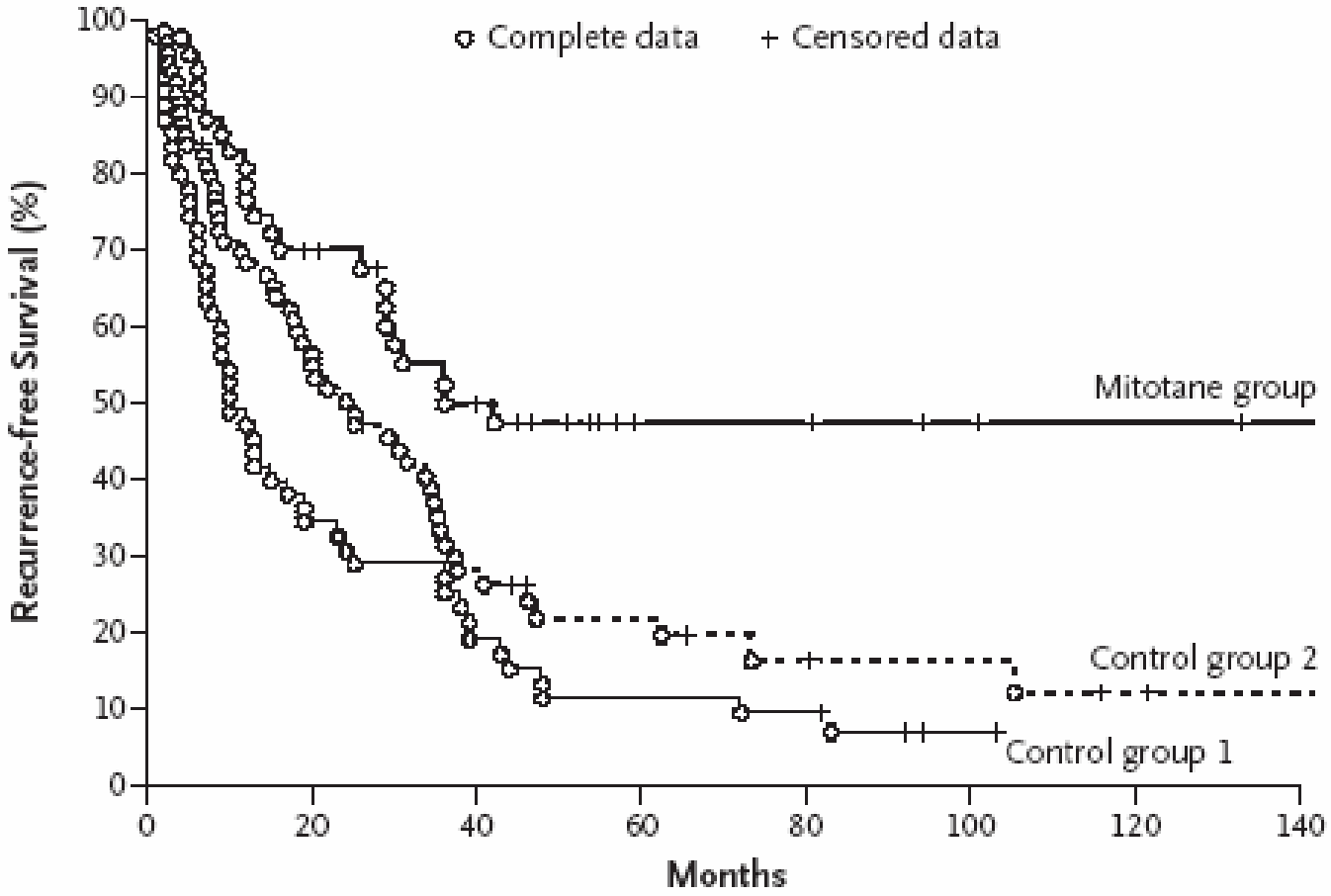
- מסקנה -

לגבי שלב א' קיימים חילוקי דעות בין המובילים בשטח בעולם הן לגבי האפשרות של ממאירות והן לגבי הצורך בטיפול המונע חזרה.

Adjuvant Mitotane Treatment for Adrenocortical Carcinoma

M. Terzolo et al, NEJM 2007; 356:2372089.

A Recurrence-free Survival

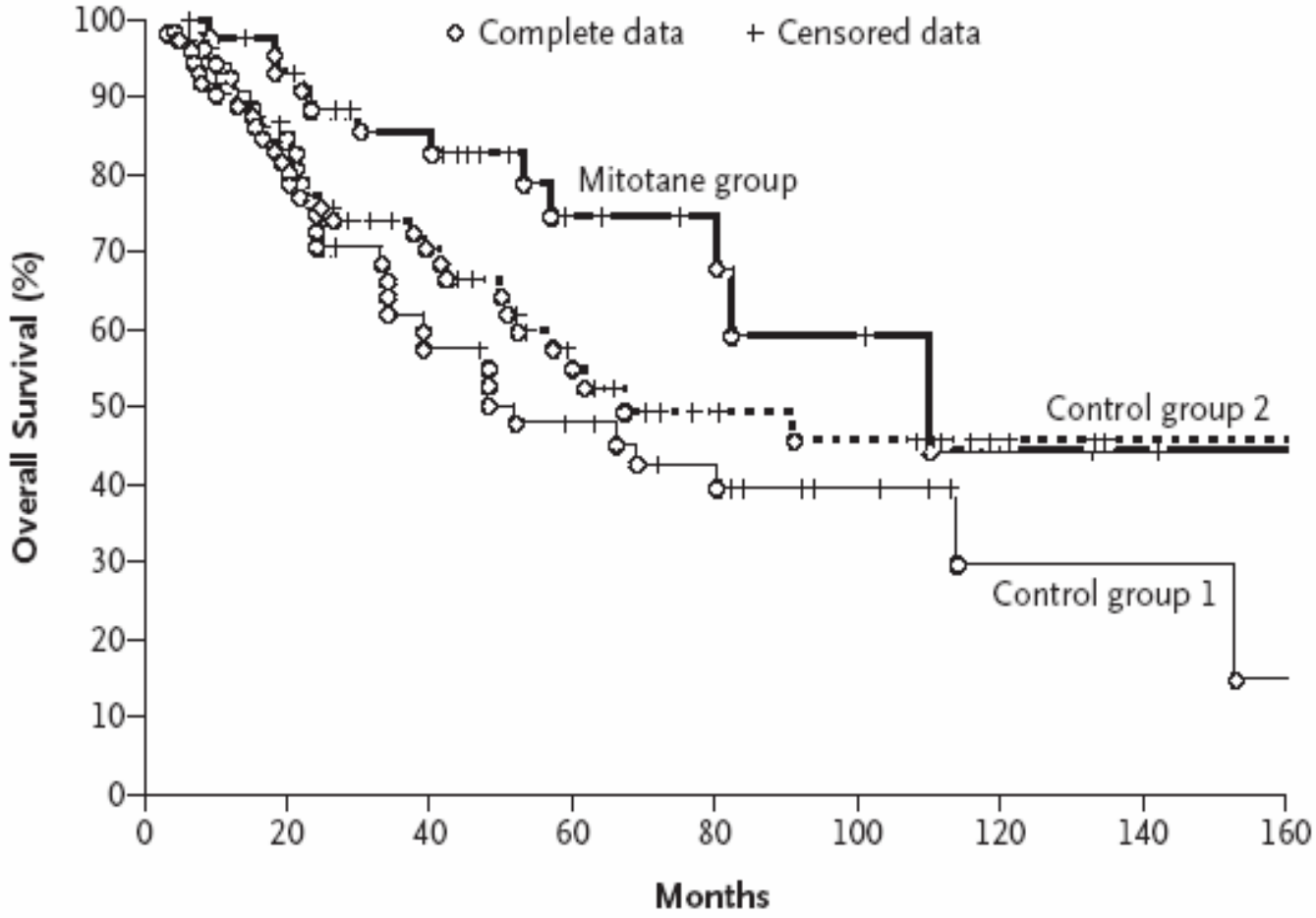


No. at Risk								
Mitotane group	47	30	20	8	5	4	2	2
Control group 1	55	19	13	6	5	1	0	0
Control group 2	75	37	15	10	5	4	2	1

Adjuvant Mitotane Treatment for Adrenocortcal Carcinoma

M. Terzolo et al. NEJM 2007; 356:2372-80.

B Overall Survival



No. at Risk									
Mitotane group	47	42	29	18	13	5	3	3	1
Control group 1	55	43	28	20	14	9	5	2	2
Control group 2	75	55	37	22	14	12	8	5	5

- תוצאות אלו מראות הבדל משמעותי במשך החיים חופשי מגידול בקבוצת הטיפול, והבדל פחות מובהק במשך החיים בכלל , במיוחד לגבי קבוצת הביקורת השנייה.
- אך האמנם ההשוואה היא נכונה?

Adjuvant Mitotane Treatment for Adrenocortical Carcinoma
Massimo Tersolo et al., NEJM;356:2372-80.

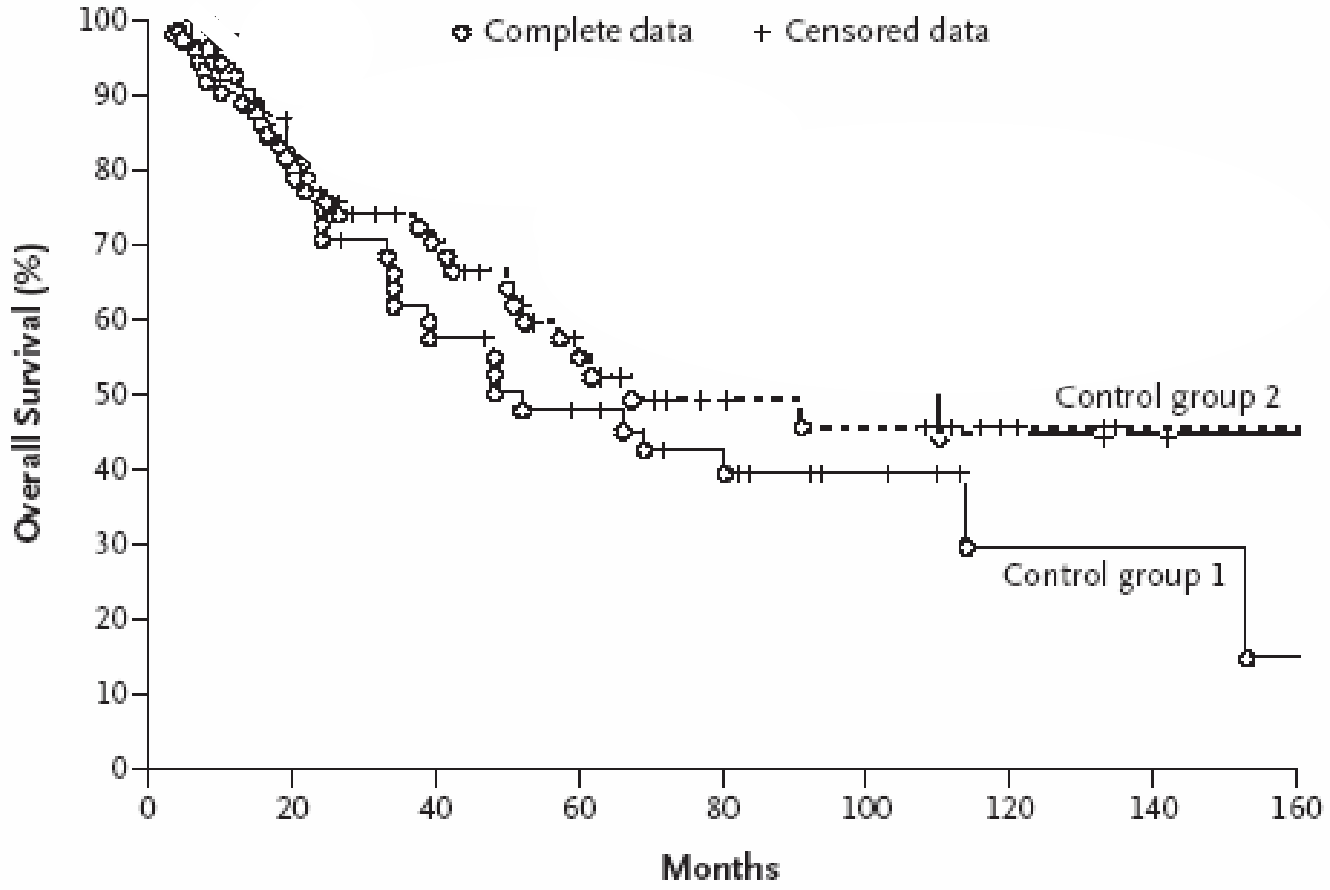
Table 1. Baseline Characteristics of the Patients.*

Characteristic	Mitotane Group (N=47)		Control Group 1 (N=55)		P Value	Control Group 2 (N=75)		P Value
Age — yr					0.30			0.03
Median	42		44			47		
Range	18–67		21–73			18–83		
Sex — no. (%)					0.05			0.1
Male	11 (23.4)		23 (41.8)			27 (36.0)		
Female	36 (76.6)		32 (58.2)			48 (64.0)		
Tumor stage — no. (%)					0.90			0.02†
I	3 (6.4)	63.8	4 (7.3)	63.7		9 (12.0)	84	
II	27 (57.4)		31 (56.4)			54 (72.0)		
III	11 (23.4)	36.2	15 (27.3)	36.4		11 (14.7)	16	
IV	6 (12.8)		5 (9.1)			1 (1.3)		

קבוצת הביקורת השנייה מורכבת מחולים הרבה יותר קלים!!

לאחר כ -10 שנות מעקב התמותה בין 2 קבוצות הביקורת משתנה מאוד!

B Overall Survival



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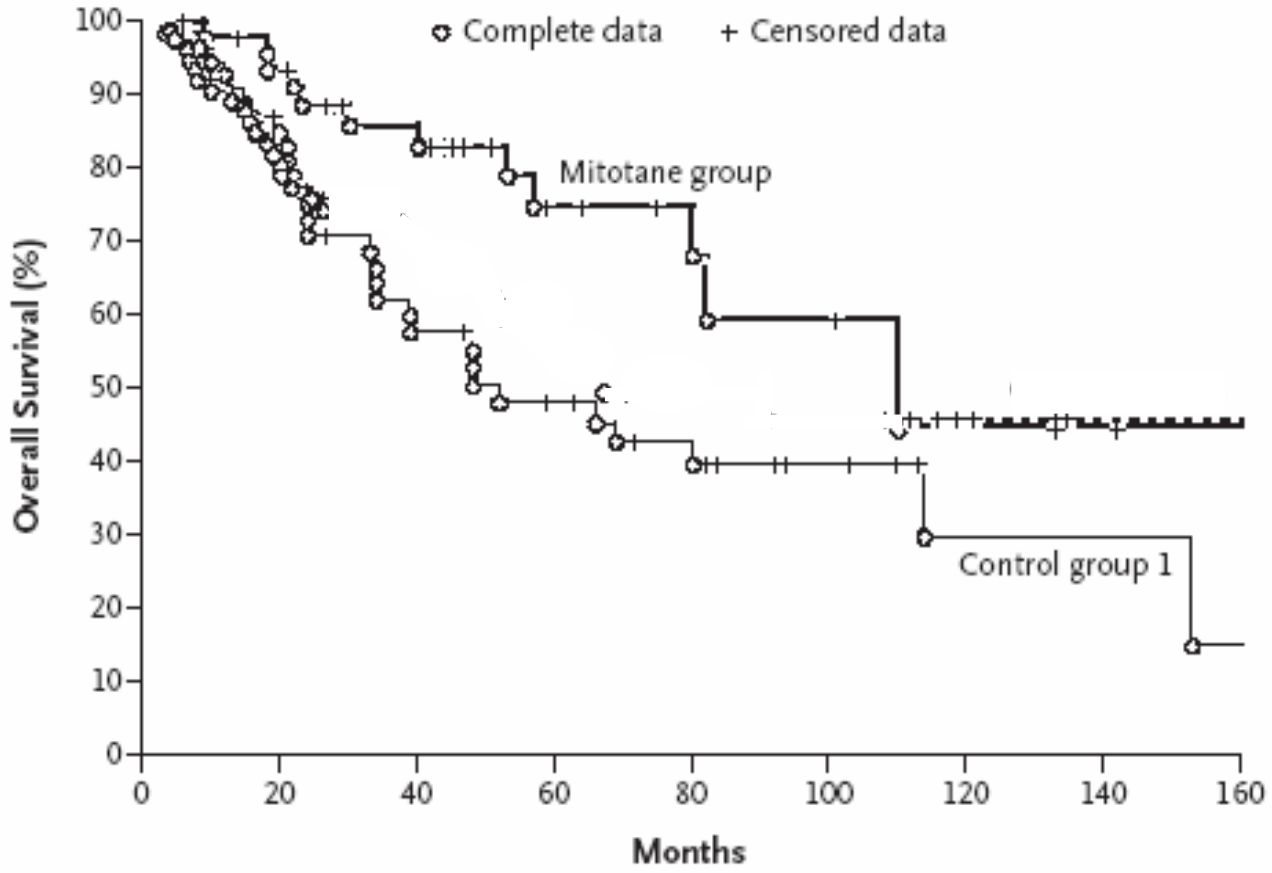
בהשוואת קבוצת הטיפול לביקורת הזהה - הבדל משמעותי !

B Overall Survival

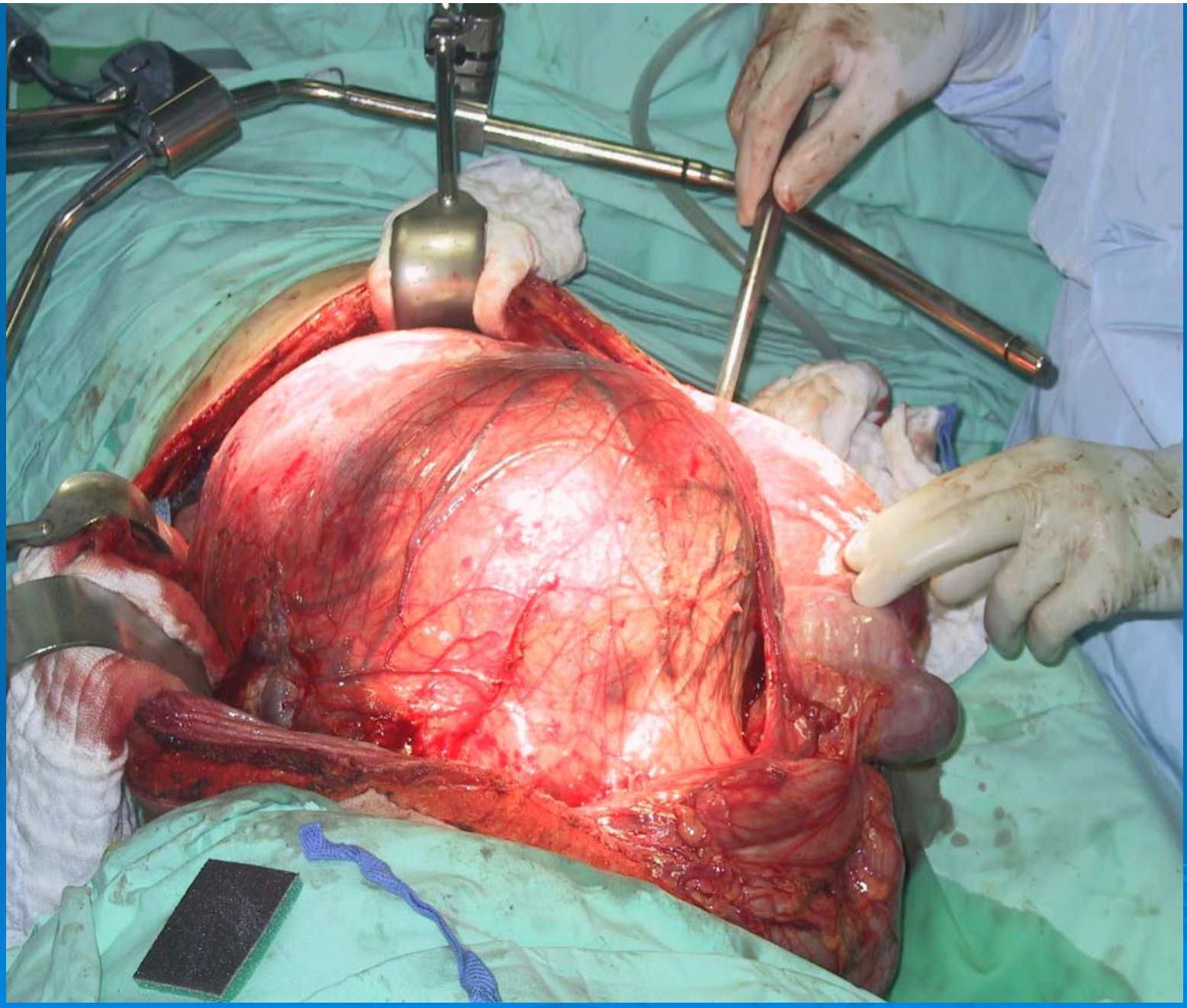


No. at Risk									
Mitotane group	47	42	29	18	13	5	3	3	1
Control group 1	55	43	28	20	14	9	5	2	2
Control group 2	75	55	37	22	14	12	8	5	5

The median recurrence-free survival was 42 months in the mitotane group, 10 months in control group 1 (P<0.001), and 25 months in control group 2 (P=0.005), according to the log-rank test.

Death from adrenocortical cancer was reported for 12 patients in the mitotane group (25.5%), 30 in control group 1 (54.5%), and 31 in control group 2 (41.3%).

דהיינו: הקטנת תמותה במעל ל -50% בהשוואה לקבוצת הביקורת הזהה, וב- 40% לקבוצת הביקורת הקלה יותר.



מראה גידול "טיפוסי"

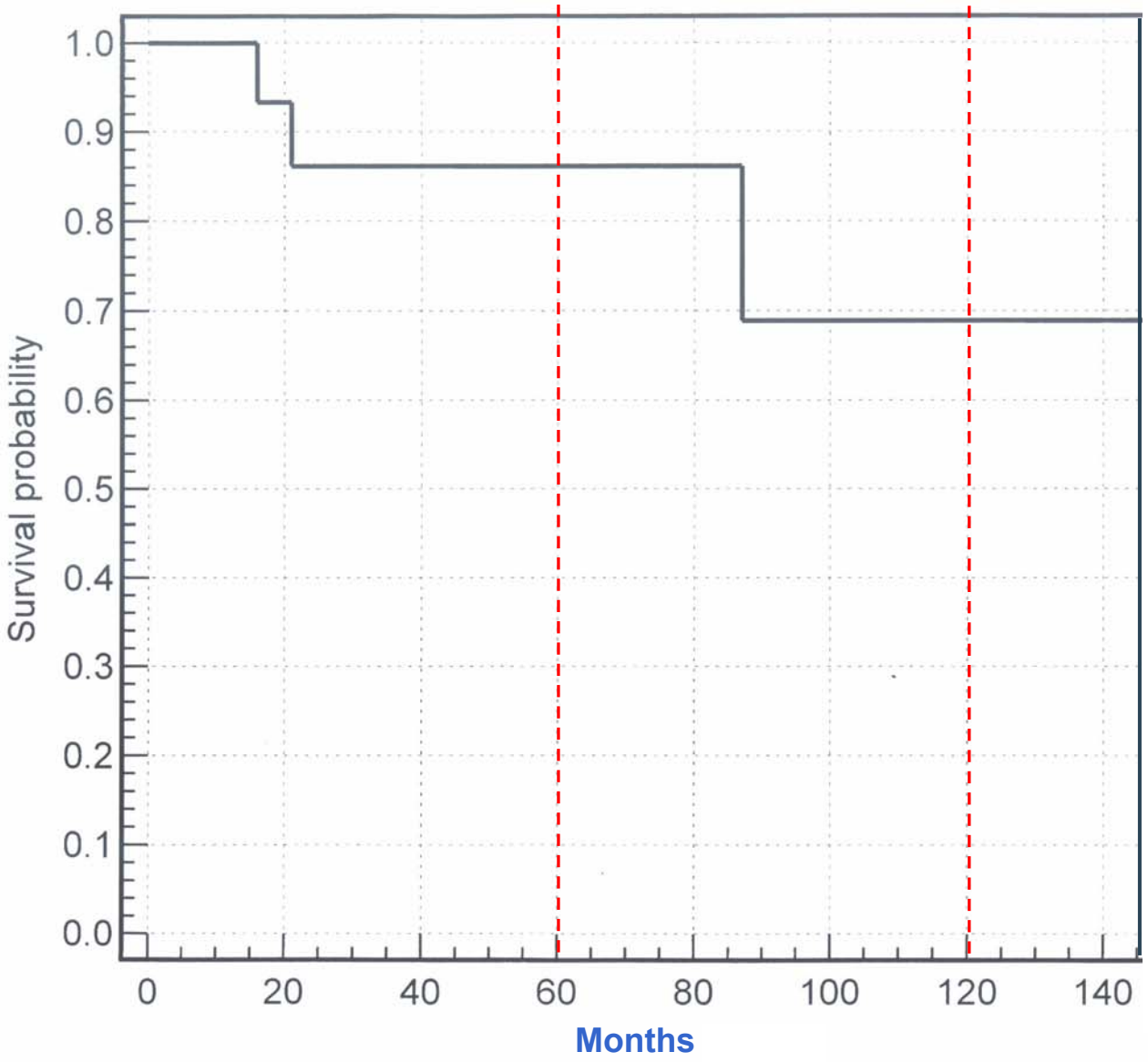
Summary – Bnai Zion results

- No of patients – 17 (60% stages III and IV)
- Tumor size - 14.1 ± 7.9 cm (4.8 – 36.0 cm)
- Tumor weight – 901 ± 631 gr (78 – 7800 gr).
- Mitotane dose – 1.5 to 3.0 gr daily
- Mean follow up – 64 months
- Still on follow up – 12 (71%)
- Unrelated death – 2 (12%)
- Death from disease – 3 (18%)
  - Improper medication – 2
  - Time till death – 12-87 months

Side effects and complications in our experience

- All patients tolerated low-dose mitotane (1.5 – 3.0 gr) well.
- One patient developed neurological signs about 5 years of treatment, reversible on discontinuation.
- One patient developed severe rise in liver enzymes after 3 months of treatment. Medication was stopped. Re-challenge caused no liver enzyme abnormalities.
- Rise in cholesterol, rise in HDL.
- Gynecomastia in males.

ACC WITH ADJUVANT MITOTANE - SURVIVAL



NO. at Risk 17 15 12 10 8 8 8 8

תוצאות בני ציון:

5y survival 85%

10y survival 70%

Chemotherapy in advanced ACC (Etoposide, Doxorubicin and Cisplatin)

Sex / Age	Stage	Size (cm)	Weight (gr)	Secret	Survival (month)
F 70	T2N0M0	17x15	620	Testo	12-died
F 45	T3N1M1	13x9	470	Cort	14-died
M46	T2N1M0	23x15	2615	None	21-died

ניסיוננו בטיפול כימותרפי משולב במיטוטן, במקרים של מחלה מתקדמת מאוד

- במאמר סיכום "טרי" מאת הקבוצה הגרמנית של מחברי המאמר ב NEJM , מוצעת סכמת טיפול הכוללת בין השאר הרחבה משמעותית באינדיקציות לטיפול במיטוטן במקרים של סרטן יותרת הכלייה.

- Best Practice and Research in Endocrinology and Metabolism, 23(2009) 273-289.

Fassnacht and Allolio, 2009

In all patients with stage I-II, and most patients with stage III, complete resection is feasible.

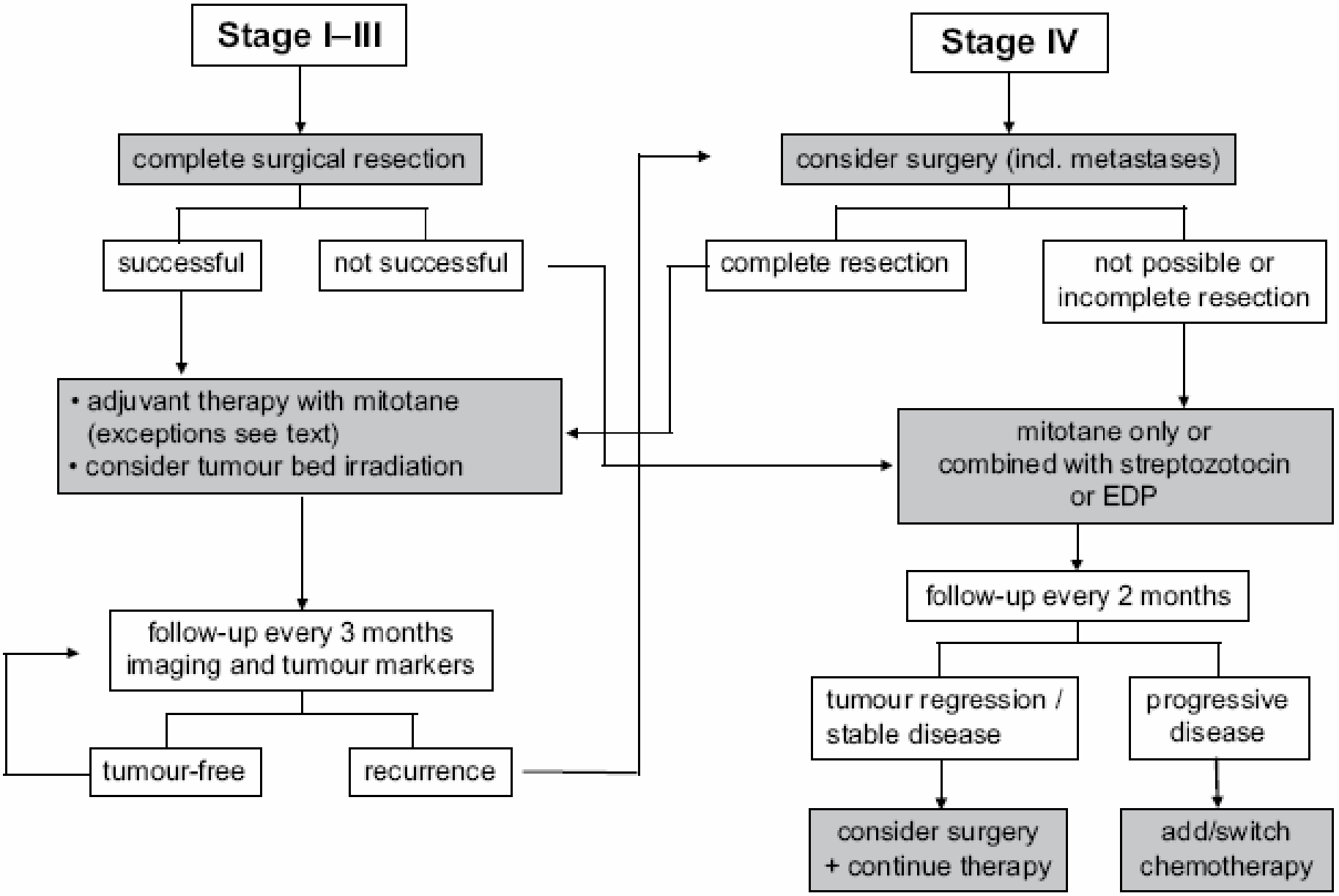
However, surgery for ACC is demanding, and expert surgeons are needed to avoid tumor spillage and incomplete resection.

In expert hands, there seems to be no difference in disease free and overall survival between laparoscopic adrenalectomy and open surgery in tumors < 10cm.

Resectable metastasis should be removed whenever possible.

Fassnacht and Allolio, 2009

- Currently, we leave patients with histologically proven ACC without adjuvant mitotane treatment only if they have a very low risk for recurrence:
- Complete tumor resection
- And tumor size < 8cm
- And no microscopic vascular invasion
- And Ki 67 < 10%


Stage I–III
complete surgical resection
successful
not successful
• adjuvant therapy with mitotane (exceptions see text)
• consider tumour bed irradiation
follow-up every 3 months imaging and tumour markers
tumour-free
recurrence
Stage IV
consider surgery (incl. metastases)
complete resection
not possible or incomplete resection
mitotane only or combined with streptozotocin or EDP
follow-up every 2 months
tumour regression / stable disease
progressive disease
consider surgery + continue therapy
add/switch chemotherapy

מחקר ADIUVO

- באחור של כ -30 שנה, ותוך ויכוחים על ההצדקה והמוסריות שבו, הוחלט לפני כשנה על ביצוע מחקר פרוספקטיבי, **עם שימוש בקבוצת ביקורת שתקבל פלצבו**, על מנת להוכיח סופית את החשיבות והיעילות של שימוש אדג'ובנטי במיטוטן בחולים עם דרגות יומרה שונות של סרטן בלוטת יותרת הכלייה

Title: "EFFICACY OF ADJUVANT MITOTANE TREATMENT IN PROLONGING RECURRENCE-FREE SURVIVAL IN PATIENTS WITH ADRENOCORTICAL CARCINOMA AT LOW-INTERMEDIATE RISK OF RECURRENCE"

(Protocol ADIUVO version January 2009)

On behalf of the European Network for the Study of Adrenal Tumors (ENS@T).

Study Rationale

- Efficacy of adjuvant mitotane treatment is suggested by a retrospective multicenter international study showing that postoperative mitotane caused significant reduction in relapse and death. These promising results need confirmation in a randomized prospective study.

- While adjuvant treatment seems justified in patients at high risk of relapse, a randomised prospective study is needed to assess whether such a treatment is efficacious in patients at low-intermediate risk.

Study Objectives - Primary:

- To compare the efficacy of adjuvant mitotane treatment *vs observation only* in prolonging recurrence free survival (RFS) in patients with ACC at low-intermediate risk of recurrence after complete resection.

Study Objectives -Secondary:

Comparison of :

1. **Overall Survival**
2. **Time to recurrence**
3. **Disease free survival**
4. **Quality of life.**
5. **Assessment of toxicity.**
6. **Assessment of the impact of mitotane serum levels on the efficacy of treatment.**

Study Design

- **Prospective, randomized, controlled, open-label, multi-center phase III trial**

Patients will be randomly assigned to receive mitotane treatment or observational follow up only. Mitotane will be administered till progression or unacceptable toxicity for a minimum of 2 years. Mitotane will be provided by HRA Pharma.

Inclusion Criteria

- Histologically confirmed diagnosis of ACC
- Low-intermediate risk of relapse defined as:
- Stage I-III ACC
- Microscopically complete resection, defined as no evidence of microscopic residual disease based on surgical reports, histopathology and post-operative imaging
- Ki 67 $\leq$ 10%
- Age $\geq$ 18 years

Treatment administered

- Patients will be randomly assigned to receive mitotane treatment or observational follow up only. Mitotane will be administered till progression or unacceptable toxicity for a minimum of 2 years. Mitotane will be provided by HRA Pharma.

Sample size and Study duration

- 200 patients (100 per treatment arm) will be recruited. The duration of the study will be: 7 years (recruitment period, 4 years; follow-up period, 3 years).