Meme kanser cerrahisinde sentinel lenf nodunu değerlendirmede intraoperatif sitolojinin tanı değeri

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Dr Mine Önenerk

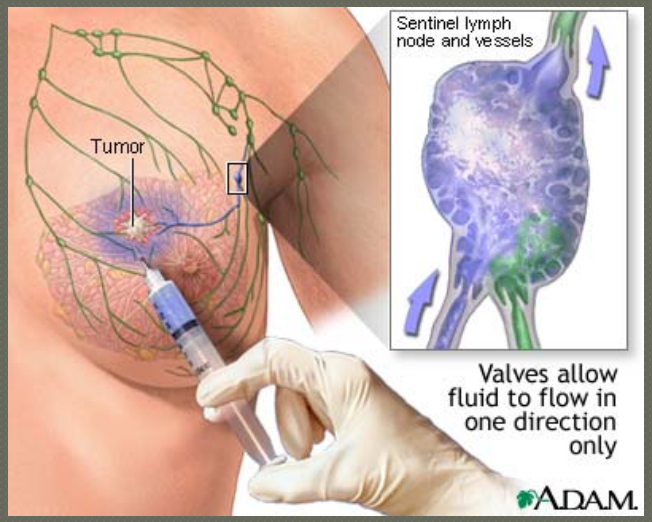
Giriş

- Aksiller lenf nodu durumu meme karsinomlarında en önemli prognostik faktörlerden biri
- Hastalıksız sağ kalım ve ortalama sağ kalım tutulan lenf nodu sayısı arttıkça azalmakta
- Tümör çapları eşit olgular gözönüne alındığında eklenen her pozitif lenf nodu mortaliteyi %6 arttırmakta

Michaelson, J.S. , American Cancer Society, 2003

Giriş

- Sentinel lenf nodu: primer tümörün metastatik hücrelerinin ilk drene olduğu lenf nodu
- İlk kez 1951 yılında total parotidektomi operasyonu sırasında kullanılmış
- Memede kullanılışı 1991 John Wayne Kanser Enstitüsünde



Tanis, P.J., Breast Cancer, 2001

Giriş

- ALND: kol disfonksiyonu, lenfödem ve ağrı
- Erken evre ve klinik nod negatif hastalarda SLND'de mikrometastaz/izole tümör hücresi varlığında ALND??

Jacobson, M.J. et al, Annals of translational medicine, 2015

ALND: Aksiller lenf nodu diseksiyonu, SLND: Sentinel lenf nodu diseksiyonu

Giriş

JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

Sentinel Lymph Node Biopsy for Patients With Early-Stage Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update

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Clinical Practice Guideline Committee approval: November 19, 2013.

Editor's note: This American Society of Clinical Oncology Clinical Practice Guideline Update provides recommendations with

A B S T R A C T

Purpose
To provide evidence-based recommendations to practicing oncologists, surgeons, and radiation therapy clinicians to update the 2005 clinical practice guideline on the use of sentinel node biopsy (SNB) for patients with early-stage breast cancer.

Methods
The American Society of Clinical Oncology convened an Update Committee of experts in medical oncology, pathology, radiation oncology, surgical oncology, guideline implementation, and advocacy. A systematic review of the literature was conducted from February 2004 to January 2013 in Medline. Guideline recommendations were based on the review of the evidence by Update Committee.

Results
This guideline update reflects changes in practice since the 2005 guideline. Nine randomized clinical trials (RCTs) met systematic review criteria for clinical questions 1 and 2; 13 cohort studies informed clinical question 3.

Recommendations
Women without sentinel lymph node (SLN) metastases should not receive axillary lymph node dissection (ALND). Women with one to two metastatic SLNs planning to undergo breast-conserving surgery with whole-breast radiotherapy should not undergo ALND (in most cases). Women with SLN metastases who will undergo mastectomy should be offered ALND. These three recommendation are based on RCTs. Women with operable breast cancer and multicentric tumors, with ductal carcinoma in situ (DCIS) who will undergo mastectomy, who previously underwent breast and/or axillary surgery, or who received preoperative/neoadjuvant systemic therapy may be offered SNB. Women who have large or locally advanced invasive breast cancer (tumor size T3/T4), inflammatory breast cancer, or DCIS (when breast-conserving surgery is planned) or are pregnant should not undergo SNB. These recommendations are based on cohort studies and/or informal consensus. In some cases, updated

Giriş

Recommendations

- Recommendation 1: Clinicians should not recommend axillary lymph node dissection (ALND) for women with early-stage breast cancer who do not have nodal metastases. Type: evidence ba… …idence quality: high. Strength of rec-ommendation: strong.
- Recommendation 2.1: Clini… …ot … …o have one or two sentinel lymph node metastases and will receive b… …tionated whole-breast radiotherapy. Type: evidence based; benefits outweigh harms. Evidence quality: high. Strength of recommendation: strong.
- Recommendation 2.2: Clinicians may offer ALND for women with early-stage breast cancer with nodal metastases found on SNB who will receive mastectomy. Type: evidence based; benefits … …low. Strength of recommendation: weak.
- Recommendation 3: Clinic… …SNB … …lowing circumstances:
- 3.1: Multicentric tumors. Type: evide…e base… …gth of recommendation: moderate.
- 3.2: Ductal carcinoma in situ (DCIS) when mas… …tweigh harms. Evidence quality: insufficient. Strength of recommendat…
- 3.3: Prior breast and/or axillary surgery. Type: evidence based; be… …idence quality: intermediate. Strength of recommendation: strong.
- 3.4: Preoperative/neoadjuvant systemic therapy. Type: evide… …as. Evidence quality: intermediate. Strength of recommendation: modera…
- Recommendation 4: There … …t data … …ot perform SNB for women who have early-stage breast cancer a…
- 4.1: Large or locally advanced invasive breast… …quality: insufficient. Strength of recommendation: weak.
- 4.2: Inflammatory breast cancer. Type: informal co… …commendation: weak.
- 4.3: DCIS when breast-conserving surgery is planned. Type: in… …uality: insufficient. Strength of recommendation: strong.
- 4.4: Pregnancy. Type: informal consensus. Evidence quality: insufficient. Strength of recommendation: weak.

1 ya da 2 sentinel lenf nodu metastazı olan ve radyoterapi alacak erken evre meme kanserli hastalarda ALND önerilmez

Kimlere SLN örnekleme yapılmalı?
1-Multisentrik tümörlere
2-Mastektomi yapılacak olan DCIS
3-Daha önceden meme veya aksiller cerrahi işlem öyküsü
4-Preoperatif /neoadjuvan sistemik tedavi

Kimlere SLN örnekleme yapılmamalı?
1-T3/T4
2-İnflamatuar meme karsinomu
3-DCIS'da MKC yapılacaksa
4-Gebelik

Amaç

- İntraoperatif SLN örneklemesi yanıtının parafin kesit sonuçları ile karşılaştırılarak yöntemin kliniğimizdeki *doğruluk, pozitif/negatif öngörü değeri, sensitivite ve spesifitesini* hesaplamak

Materyal ve metodlar

- HNEAH'nde 2002-Mayıs 2015 tarihleri arasında meme karsinomunda, sitolojik (imprint ve squash) yöntemler ile değerlendirilen sentinel lenf nodu örneklemesi yapılmış **522** olgu

Materyal ve metodlar

- Frozen sırasında:
- 2 mm'lik kesitler
- Her kesit yüzünden imprint /squash preparatlar hazırlanarak H&E ile boyanıyor
- Parafin:
- 10 seri kesit; 8 H&E
- 2 ile 8. kesitlere Pan-K

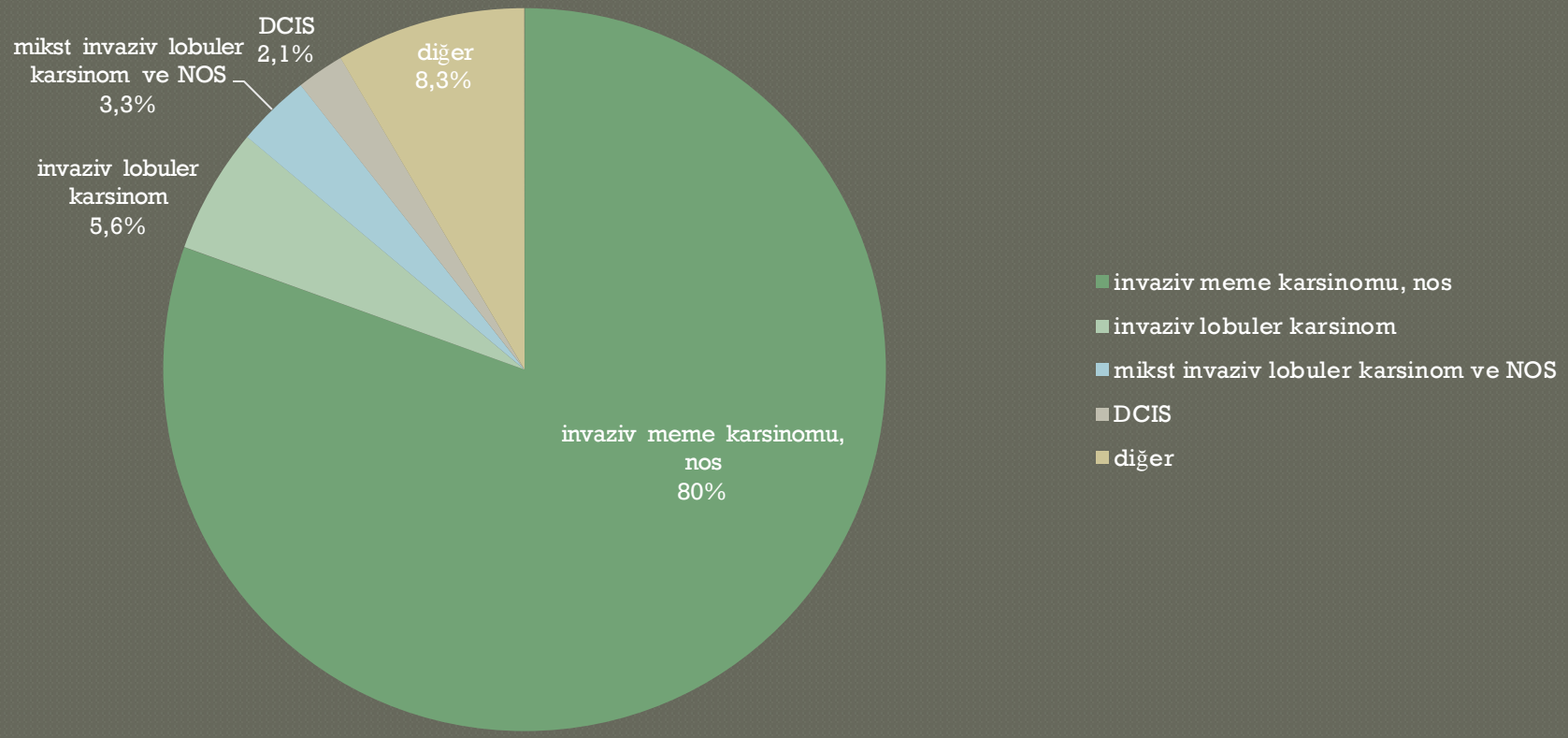
Sonuçlar

Tablo 1- Hasta karakteristikleri	
Cinsiyet	**K: 521,** E: 1
Yaş	Ortalama: 55 (30-87 yaş)
Lokalizasyon	Sağ: % 43,7 (n=229) Sol: %55,2 (n=289) Bilateral: %0,76 (n=4)
Cerrahi tipi	Mastektomi: %44,2 **Meme koruyucu: %55,8**
Tümör çapı	**Ortalama: 2,26 cm** (0,07-10cm)

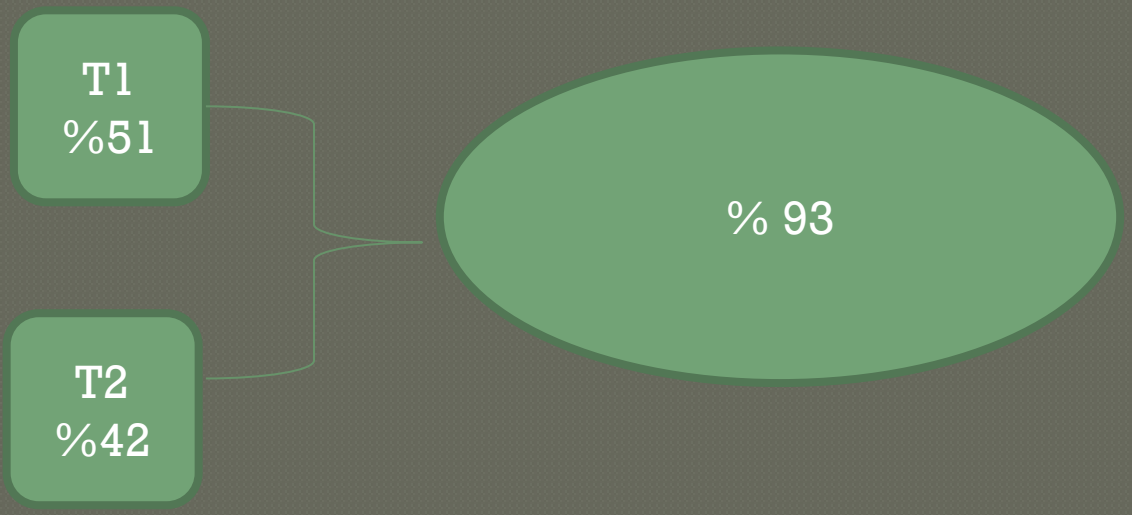
Sonuçlar

Tablo 2- Tümör tipleri	
İnvaziv meme karsinomu, NOS	%80 (n=417)
İnvaziv lobuler karsinom	%5,6 (n=29)
Mikst lobuler ve invaziv meme karsinomu, NOS	%3,3 (n=17)
Müsinöz karsinom	%3,1 (n=16)
Metaplastik karsinom	%1,7 (n=9)
Medüller karsinom	%1,2 (n=6)
Apokrin diferansiasyon gösteren İnvaziv meme karsinomu	%0,8 (n=4)
Tubuler karsinom	%0,6 (n=3)
Kribriform karsinom	%0,4 (n=2)
İnvaziv papiller karsinom	%0,6 (n=3)
Adenoid kistik karsinom	0,2 (n=1)
DCIS	%2,1 (n=11)

Sonuçlar

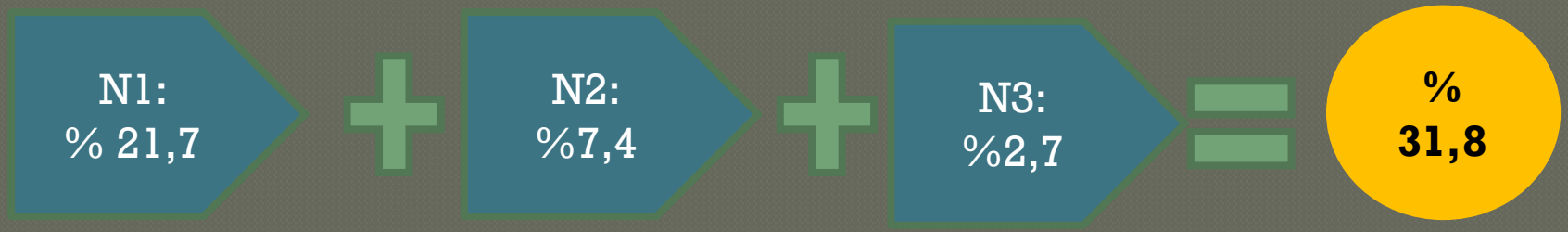

DCIS
2,1%
diğer
8,3%
mikst invaziv lobuler karsinom ve NOS
3,3%
invaziv lobuler karsinom
5,6%
invaziv meme karsinomu, nos
80%
invaziv meme karsinomu, nos
invaziv lobuler karsinom
mikst invaziv lobuler karsinom ve NOS
DCIS
diğer

Sonuçlar



*T3: %4 T4: % 0,8 Tis: %2,1

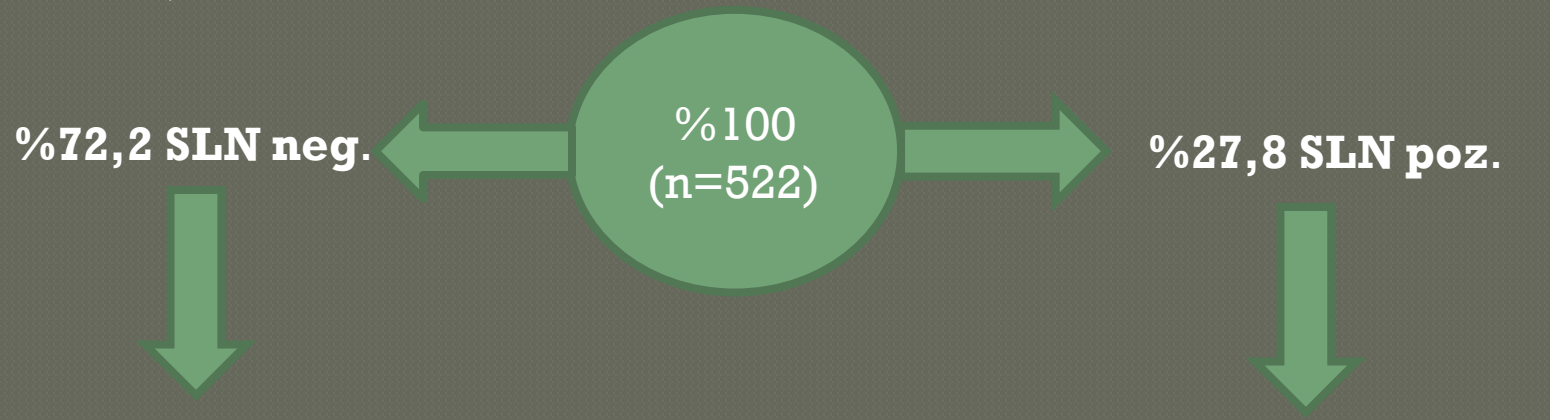
Sonuçlar



* N0: % 58,4

Sonuçlar

- Örneklenen lenf nodu sayısı: 2,6 (1-9)
- Metastaz çapı: ortalama 8,9 mm
- Yanlış pozitif olgu yok
- 27 olgu yanlış negatif (izole tm hücreleri dahil)



Sonuçlar

Tablo 5- Yanlış negatif olguların incelenmesi	
İzole tümör hücresi	%25,9 (n=7)
Mikrometastaz	**% 66,7 (n=18)**
Makrometastaz	% 7,4 (n=2) (metastaz çapı: 2,4 ve 2,7 mm)

Sonuçlar:

	sensitivite	spesifite	ppv	npv	doğruluk
ITH YN olgulara dahil edildiğinde	***%84,3***	*%100*	*%100 (CI=97,4-99,9)*	*%93 (CI=89,8-95,3)*	***%94,8***
ITH YN olgulara dahil edilmediğinde	***%87,9***	*%100*	*%100 (CI=97,4-99,9)*	*%95 (CI=92-96,5)*	***%96,2***

ITH: izole tümör hücresi, YP: yanlış negatif, ppv/npv: pozitif/negatif prediktif değer

Sonuçlar

	Gerçek pozitif (n)	Yanlış negatif (n)	Sensitivite
Makro	138	2	***%98,5***
Mikro	42	*18	***%57,1***
İTH	10	**7	***%30***

*24 olguda mikrometastaz SLN saptandı
**3 olguda ITH saptandı

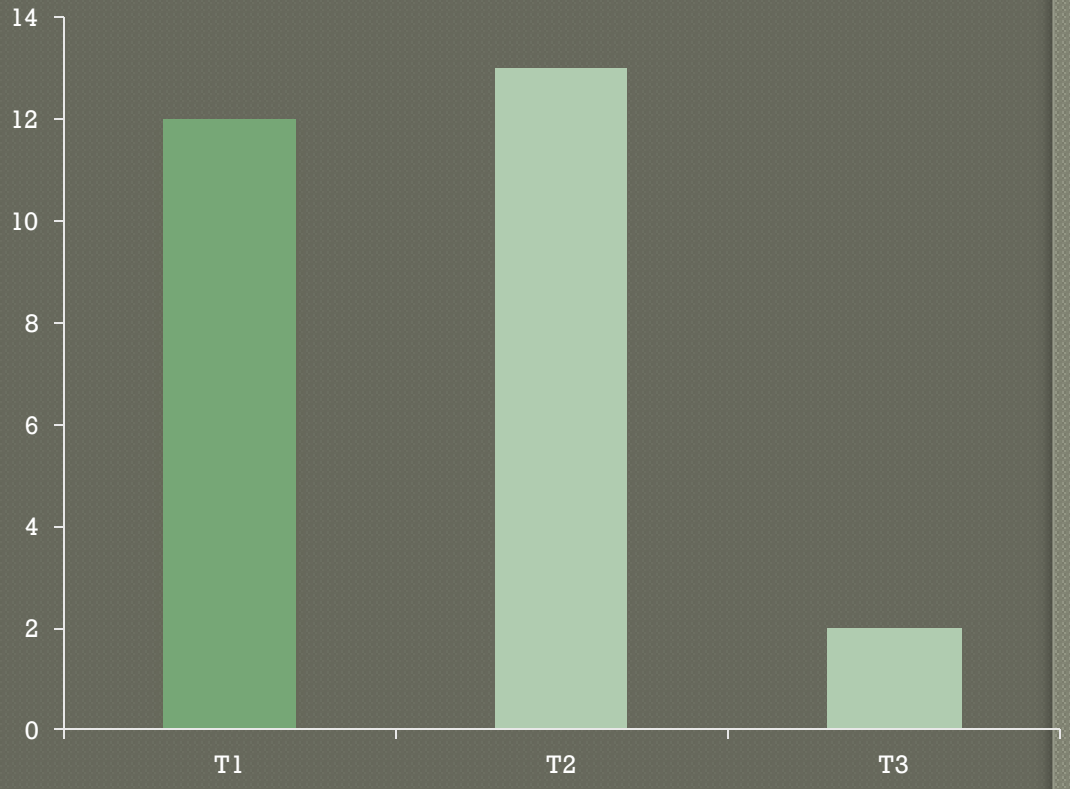
Sonuçlar

Yanlış negatif olgular;

- 24 invaziv meme karsinomu, NOS
- 1 invaziv lobuler karsinom
- 1 mikst invaziv lobuler ve meme karsinomu, NOS
- 1 metaplastik karsinom

Sonuçlar

Yanlış negatif olgular;
Ortalama tümör çapı: 2,2 cm
Makrometastaz saptanan olgular T1 ve T2



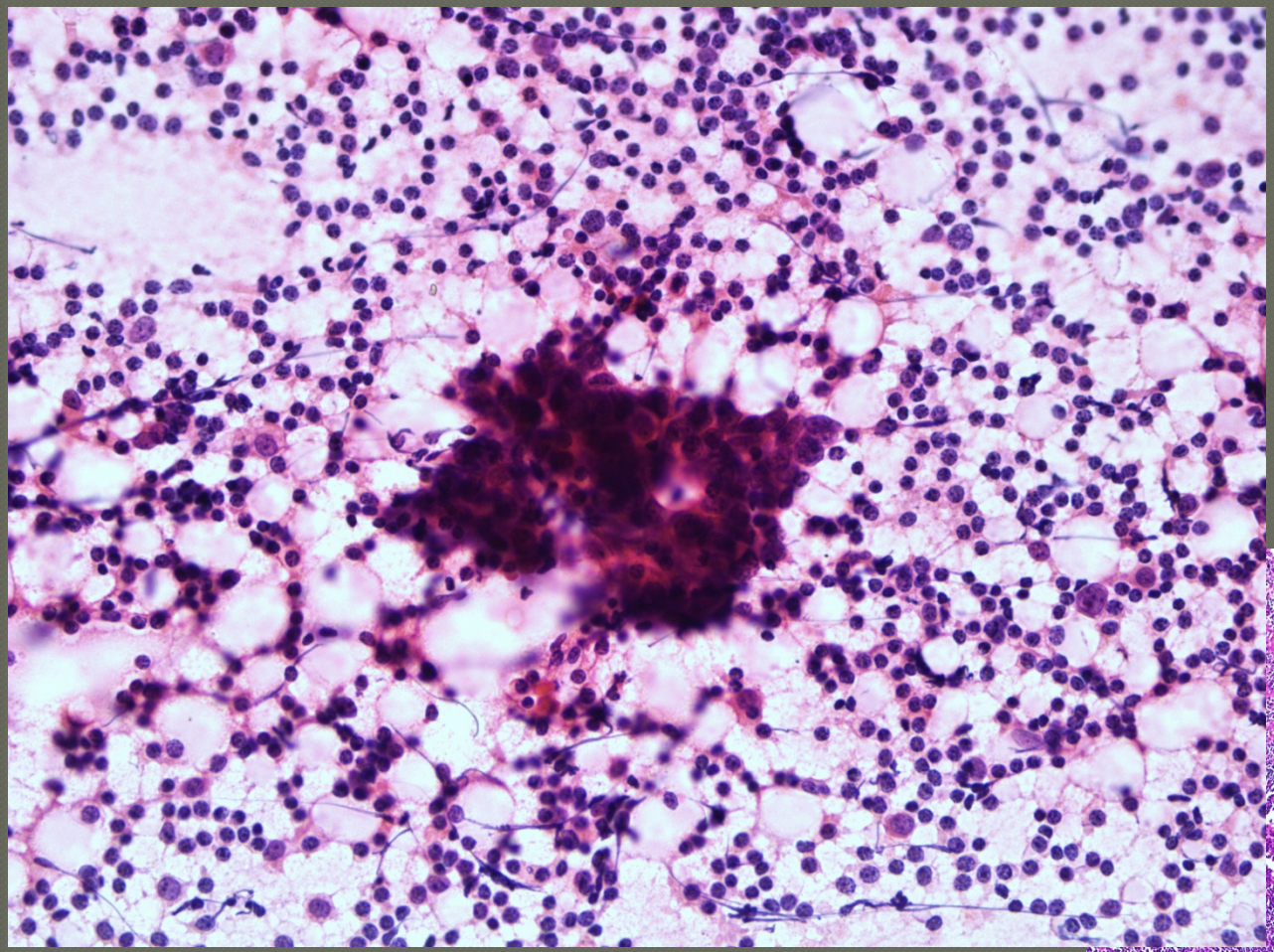
Sonuçlar

ALND yapılan YN olgular;

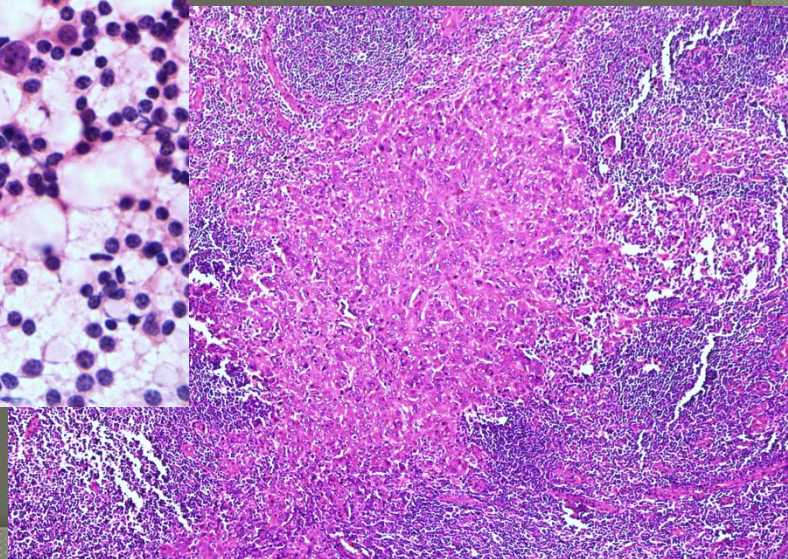
- 2 makrometastazlı olgudan birinde başka pozitif lenf nodu saptanmadı. Diğerinde 1 adet lenf nodu pozitifti (met çapı: 2,9 mm).
- 2 mikrometastazlı hastada başka pozitif lenf nodu saptanmadı.
- 1 mikrometastazlı hastada aksiller lenf noduna 1 yıl sonra İİAB yapıldı; sonuç negatif

İİAB: ince iğne aspirasyon biyopsisi

Sonuçlar



- Yorumlama hatası olan tek vaka
- Diğer olgularda yaymalarda tm hücresi yok



Tartışma

	FROZEN KESİT			SİTOLOJİ			
	Andrío et al 2015 (n=370)	Fancellu et al 2012 (n=1021)	Horvath et al 2009 (n=264)	Dabbs et al 2004 (n=748)	Karamlou et al 2003 (n=142)	Richards Et al 2011 (n=230)	*HNEAH (n=522)*
sensitivite	%67	%91,6	%70	%45	%75,3	%38,5	*%87,9*
spesifite	%100	%100	%100	%99	%100	%100	*%100*
ppv	%100	%100	%100	%99	%100	%100	*%100*
npv	%95	%96,0	%85	%80	%95,1	%74,2	*%95*
doğruluk	%95	%97,0	%89	%85	-	%88,7	*%96,2*

Tartışma

	sitoloji	**frozen kesit**	**frozen kesit+sitoloji**	***HNEAH***
sensitivite	%70,3	%75,7	%89,2	*%87,9*
spesifite	%98,6	%100	%100	*%100*
ppv	%96,3	%100	%100	*%100*
npv	%86,8	%89,1	%94,8	*%95*
doğruluk	%89,1	%91,9	%96,0	*%96,2*

Lumachi, F., Anticancer Research 2012

One-step nucleic acid amplification:

- CK 19 mRNA ile SLN örneklenmesinde metastaz (< 250 kopya: negatif)

EDITOR'S CHOICE

Intraoperative analysis of sentinel lymph nodes in breast cancer by one-step nucleic acid amplification

Gábor Cserni

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ABSTRACT

One-step nucleic acid amplification (OSNA) is a novel method introduced for the lymph node staging of breast cancer and has been tested in multiple series. The present review summarises current literature and concerns related to the new method. The results of this automated molecular assay based on the quantification of cytokeratin 19 mRNA show a 96% concordance rate with detailed histopathology complemented with immunohistochemistry when alternative slices of the same lymph node are used for the two tests. The low false-negative rate makes OSNA suitable for the intraoperative evaluation of sentinel lymph nodes. The false-positive rate also seems very low. Most discordant cases are explainable by low volume metastases (micrometastases), which may be missing from the material submitted for one test, but not from the different part used for the other test. It is tempting to change the gold standard for comparisons between the methods, and if this is done, histology seems to come

cially prone to remain occult during intraoperative assessment.[3 4] It ensues that the sensitivity of intraoperative pathology is less than optimal, despite a very good specificity of approximately 99–100%. A meta-analysis of 31 studies on imprint cytology suggested an overall sensitivity of 63%; the pooled sensitivity for macrometastases was higher (81%) than that for micrometastases (22%).[3] A similar meta-analysis of 47 series of intraoperative frozen sections reported a pooled sensitivity of 78%; again sensitivity for macrometastases (94%) was higher than that for micrometastases (40%).[4]

To improve on this, several initiatives were tested. Multilevel serial frozen sectioning,[5] rapid immunohistochemistry applicable with both intraoperative cytology specimens[6 7] and frozen sections[8–10] have all resulted in increased sensitivity and time requirement. As an alternative way of intraoperative SLN investigation, molecular

Tartışma

Table 4 Results of histological and OSNA tests in different validation series, OSNA being the gold standard for comparison

Reference (first author)	SENS	SPEC	ACC	PPV	NPV	FNR	FRR
Tsujimoto[12]	95.6	99.3	98.8	95.6	99.3	4.4	0.7
Visser[24]	88.4	98.9	96.8	95.3	97.1	11.6	2.9
Schem[25]	87.4	100	95.5	100	93.4	12.6	6.6
Tamaki Trial1[26]	86.4	99	96.8	95	97.1	13.6	2.9
Tamaki Trial2[26]	77.8	99.4	95	97.2	94.6	22.2	5.4
Snook[18]	86.8	98.1	95.9	91.7	96.9	13.2	3.1
Feldman[27]	84.3	96.7	95.1	78.1	97.8	15.7	2.3
Bernet[28]	94.3	99.3	98.2	97.1	98.6	5.7	1.4
Le Frere-Belda[14]	81	98.8	96.5	91.1	97.2	19	2.8
All	**85.8**	**98.3**	**96.1**	**91.7**	**97**	**14.2**	**3**

ACC, accuracy (concordance rate of the two tests); FNR, false-negative rate (false-negatives/all positives); FRR, false-reassurance rate (false-negatives/all testing negative); NPV, negative predictive value; OSNA, one-step nucleic amplification; PPV, positive predictive value; SENS, sensitivity; SPEC, specificity; values expressed as percentages.

Tartışma

	Frozen kesit		Sitoloji	OSNA	HNEAH (sitoloji)
	Sanguinetti 2014 (n=278)	Andrío et al 2015 (n=370)	Chen et al 2011 (n=366)	Chen et al 2013 (n=522)	(n=522)
Mikro+ ITH	%40	%33	%28,6	%50	%51,9

Tartışma

- Yanlış negatif olgularımızın çoğu mikrometastaz ve izole tümör hücresi varlığı → literatür ile benzer
- Sadece sitolojik değerlendirme ile elde edilen sensitivite ve spesifite *sitoloji+frozen kesit* ve sadece *frozen kesit* yapılarak incelenen çalışmaların sonuçları ile örtüşmekte

Tartışma

- Serilerde SLN ile saptanan mikrometastaz %2-%23, İTH %8,9-%10,6

- Non sentinel lenf nodu tutulumu;
- *Makrometastaz: %46-%80*
- *Mikrometastaz: %0-%80*
- *ITH: %4-%19*

- Mikrometastaz ve ITH varlığında ALND yapılması konusunda tartışmalı görüşler tartışmalı; ortalama sağkalım, hastalıksız sağkalım ve lokal rekürrensi etkilemediğine dair çalışmalar mevcut

Cedollini, C., Int J Clin Exp Pathol (2014)
Francissen C.M.T.P., Ann Surg Oncol (2012)

Tartışma

Sitoloji:

- Hızlı
- Ucuz
- Doku korunumu
- Artefakt oluşumuna neden olmaz
- Çok sayıda slide hazırlanabilir

Frozen kesit:

- Zaman alır
- Daha pahalı
- %50'ye ulaşabilen doku kaybı
- Donma artefaktı
- Seri kesit yapılması zaman alacağından sınırlı kesitle değerlendirme

- Teşekkürler…