Radioterapia dopo svuotamento ascellare: quando?

Radiotherapy after axillary dissection: when?

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Post-operative Node RT

High-risk patients N+ ≥4

Mastectomy and breast conserving surgery

Recht A et al, ASCO GuidelinesJ Clin Oncol 2001 19:1539-1569

Eifel P et al. Consensus Development Panel, J Natl Cancer Inst 2001, 93:979-989

Truong P. et al. CMAJ 2004, 170:1263-1273

- Reduces local-regional relapse
- Improve survival

Overgaard M et al. N Engl J Med 1997, 337:949-955

RagazJ et al. N Engl J Med 1997, 337:956-962

WhelanT et al. J Clin Oncol 2000, 18:1220-1229

Clarke M et al. Lancet 2005, 366:2087-2106

Which nodes need to treat?

- Wide variation in clinical practice adjuvant RT

  IMN in Europe, SC +A in North American

  Ceilley E et al. Int J Radiat Oncol Biol Phys 2005, 61:365-373
  Clavel S et al. Clin Oncol 2010, 22:39-45

- Increased risk of side effects

  Truong PT et al. CMAJ 2004, 170:1263-1273
  McCready DR et al. Axillary dissection. Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer CMAJ 1998, 158:S22-S26

Which nodes need to treat?

Supraclavicular nodes → Certainly

Internal mammary nodes → Unclear

Axillary nodes

Recht A. et al. J Clin Oncol 2001, 19:1539-1569
Kunkler IH. Breast 2009, S3:S112-S120
Truong P. et al.CMAJ 2004, 170:1263-1273

Postmastectomy R trials RT given to all nodes
High Axillary Relapse rate

Overgaard M et al. N Engl J Med 1997, 337:949-955
Ragaz J et al. N Engl J Med 1997, 337:956-962

Regional relapse in early breast cancer
RM and BCS no RT

320 pts 11 ln asport 3 LN +

Sites relapse	%
Local	18,7%
Axilla	7%
Supraclavicular	7%
Mammary nodes	0,3%
Multiple	3,1%

Fisher B et al. Int J Radiat Oncol Biol Phys 1997, 3:541-550

AR strongly associated with local R

Harris EER et al. Cancer 2003, 98:2144-2151

Regional relapse in early breast cancer
BCS/RM + adjuvant TP

Sites 1st relapse	%	pts 2509
Local-regional	35.8	
Local	27.2	
Axilla	3.1	
SC	5.5	
Distant	64.2	

RR Rate at 1-2-3 and 10 ys: 3.5%, 5%, 4.2%, 3.5%

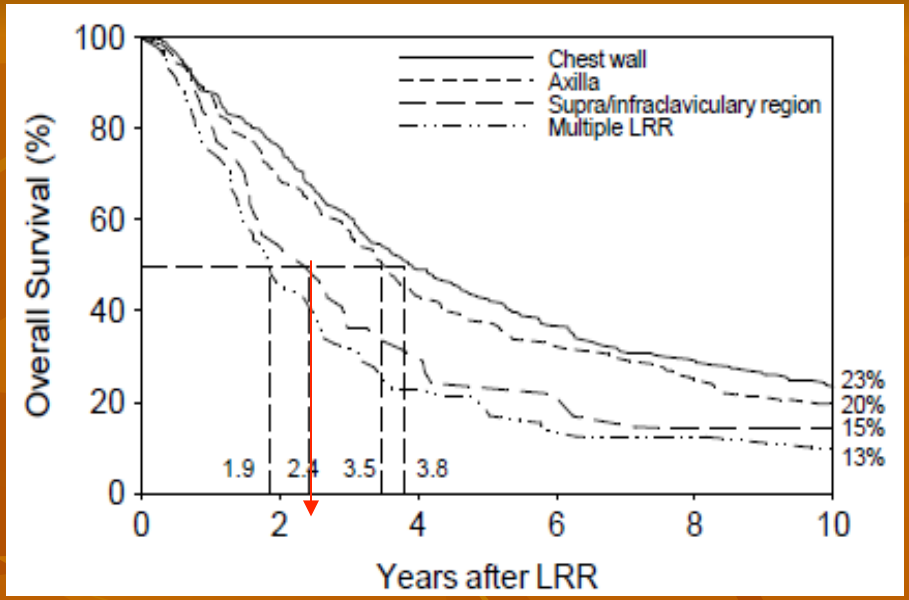
Elder EE et al. EJSO 32:922-927, 2006

Prognosis axillary relapse

RM

SM 3.5 ys

Nielsen HM et al. Radiother Oncol 2006, 79:147-155



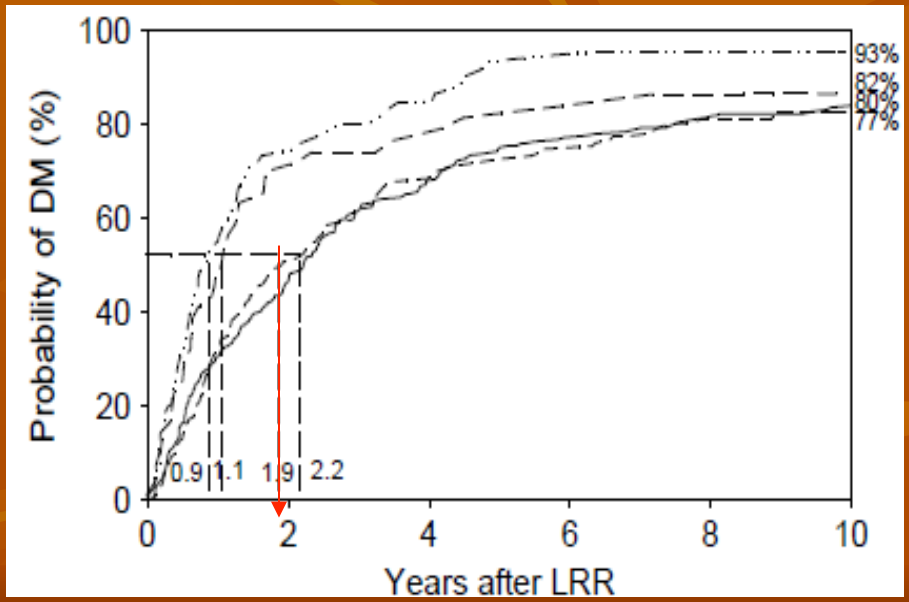
From Nielsen HM et al. Radiother Oncol 2006, 79:147-155, modified

BCS

2669 pts NSABP

DDFS 5 ys 12.1%

Wapnir IL et al. NSABP J Clin Oncol 24:2028-2037, 2006



Axillary dissection

- Standard lymphadenectomy: Level I and II nodes
  (lateral and below to and deep to pectoralis minor muscle)
- Accurate staging
- Seldom significant lymphedema
- ≥ 10 Nodes must be removed: correct stage 97% pts
- AR Risk inversely related to number of removed nodes

McCready DR et al. Axillary dissection. Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer CMAJ 1998, 158:S22-S26

Axillary Relapse: Risk Factors

1) Removed nodes
2) Positive nodes
3) Positive/examined nodes
4) Bio-pathological Factors (Tm size, grade…)
5) Extracapsular extension
6) Axillary apex involvement

Recht A., Houlihan MJ. Cancer 1995, 76:1491-1512
Katz A et al. J Clin Oncol 2000, 18:2817-2827
Nielsen HM et al. Radiother Oncol 2006, 79:147-155
Recht A. et al. J Clin Oncol 2001, 19:1539-1569

NUMBER OF EXAMINED NODES
Axillary relapse after BCS

Author	ptsz	removed nodes	R %
Harris EER et al. 2003	1293	15	1,6%
Livi et al. 2006	4185	16	0,33%
Wapnir IL et al. 2006 NSABP B-15,16,18,22,25	2669	I-II Lev	1,7%
Galimberti V et al. 2008	287	24	0,4%
Fowble B et al. 1989	990	I-II lev	1,7%
Galper S et al. 1999	691	11	1,2%
Recht A et al. JCO 1991	1624	I-II lev	2.1

NUMBER OF EXAMINED NODES
Axillary relapse after mastectomy whithout RT

Author	pz	removed nodes	rate
Nielsen et al.* DBCG 82b/c 2006	1545	7	11%
Strom et al.* 2005	1031	17	3% 10 ys
ECOG* Recht 1999	2016	15	2.2%
Fowble et al.* 1988 ECOG	627	I-II Lev	1,2%
Botteri et al. 2012	650	20	0,8%
Livi et al. 2007	2064	19	0,8%
Truong P et al. Red J 2005	821	10	4,3%
Wallgren A et al.* 7 IBCSG, 2003	5352	>8	3.6%

Randomized trials vs other trials

- 15-17 LN removed in large studies

Recht A et al. J Clin Oncol 1999, 17:1689-1700
Katz A et al J Clin Oncol 2000, 18:2817-2827
Wallgreen A et al. J Clin Oncol 2003, 21:1205-1213
Taghian A et al. J Clin Oncol 2004, 22:4247-4254

vs

- 7 e 11 LN in randomized trials

Overgaard M et al. N Engl J Med 1997, 337:949-955
Ragaz J et al. N Engl J Med 1997, 337:956-962

- Discrepancies definition LRR
- Adjuvant chemotherapy

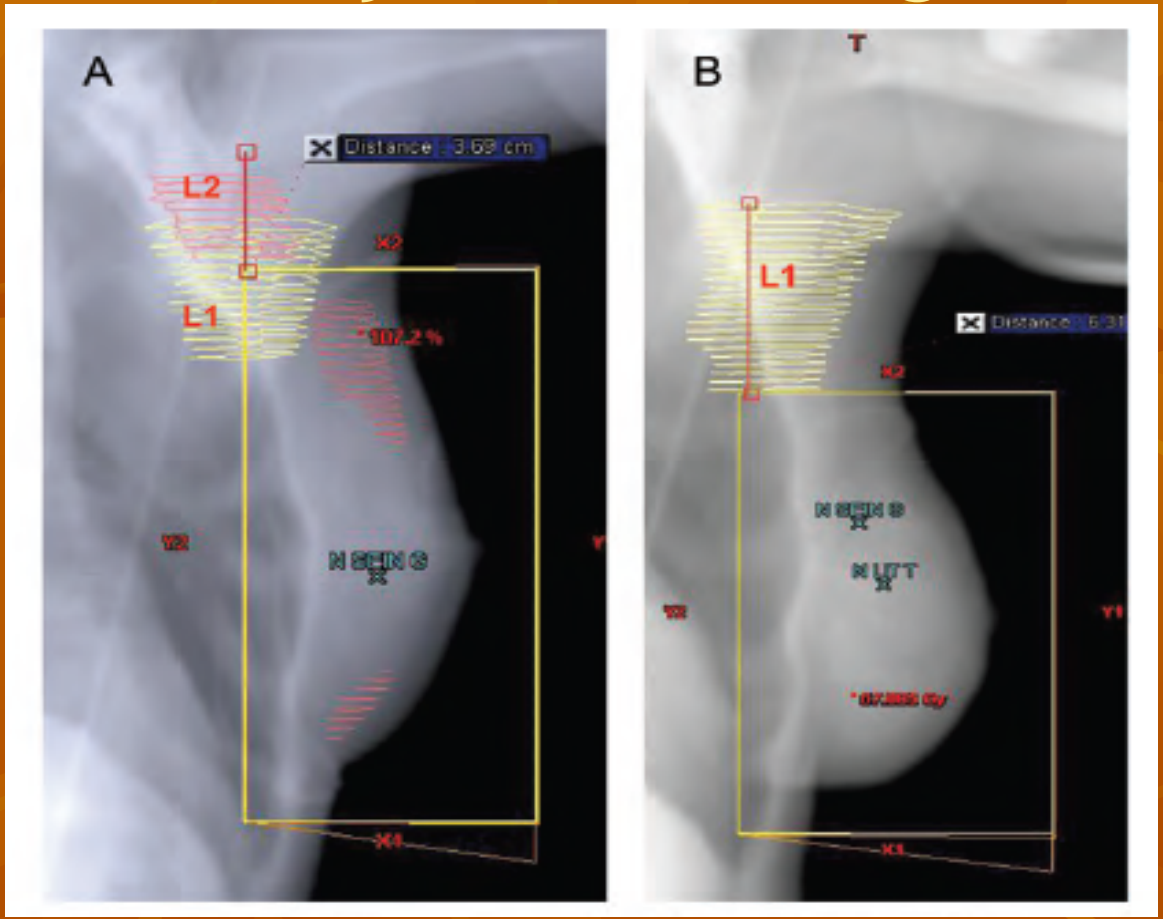
Recht A et al. ASCO GuidelinesJ Clin Oncol 2001 19:1539-1569
Taghian A et al. J Clin Oncol 2004, 22:4247-4254

Is axilla irradiated by standard tg breast fields?

pts BCS axillary clips as surrogate for nodes

- 38% all clips included
  McCormick B et al. J Surg Oncol 2002, 81:12-16
- Median dose level I → 38.5 Gy
- Median dose level II → 20.6 Gy
  Aristei C et al. Int J Radiat Oncol Biol Phys 2001, 51:69-73
  Belkacemi Y et al . Ann Oncol 2013, 24:2023-2028
- TG fields 95% dose to 51% level 1 and 26% level 2 axillary nodes
  Reznik J et al. Int J Radiat Oncol Biol Phys 2005, 61:163-168

Is axilla irradiated by standard tg breast fields?



From Belkacemi Y et al. Ann Oncol 2013, 24:2023-2028, modified

Tangent fields for breast RT do not entirely include level I-II axillary nodes

Reed DR et al. Int J Radiat Oncol Biol Phys 2005, 61:358-364
Schlembach PJ et al. Int J Radiat Oncol Biol Phys 2001, 51:671-678

NUMBER OF POSITIVE NODES Axillary relapse

Author	pz	removed nodes	positive nodes m	FU	rate
Sharma R et al. Ann Surg Oncol 2010	1019	16	0-3	7.47 ys	0,1
Stranzl H et al. 183 Strahlenther Onkol 2004	12	1-3	44.4 ms	0,6	
Galper S et al. Red Journal 1999	691	11	0-3	8 ys	1,2
Galimberti V et al. Tumori 2008	287	24	7	5 ys	0,4
Perrucci E et al. Tumori 2004	86	22	14	36.5 ms	2.3

NUMBER OF POSITIVE NODES Axillary relapse

- 313 N0
- mFU >5 ys
- 16 LN removed
- 0,3%

Taghian A et al. J Clin Oncol 2004, 24:3927-3932

5758 N+ median 3

mFU 11 ys

16 LN removed

1,4%

Taghian A et al. J Clin Oncol 2004, 22:4247-4254

650 RM no RT I-II Lev

FU 65 m

N0 0%

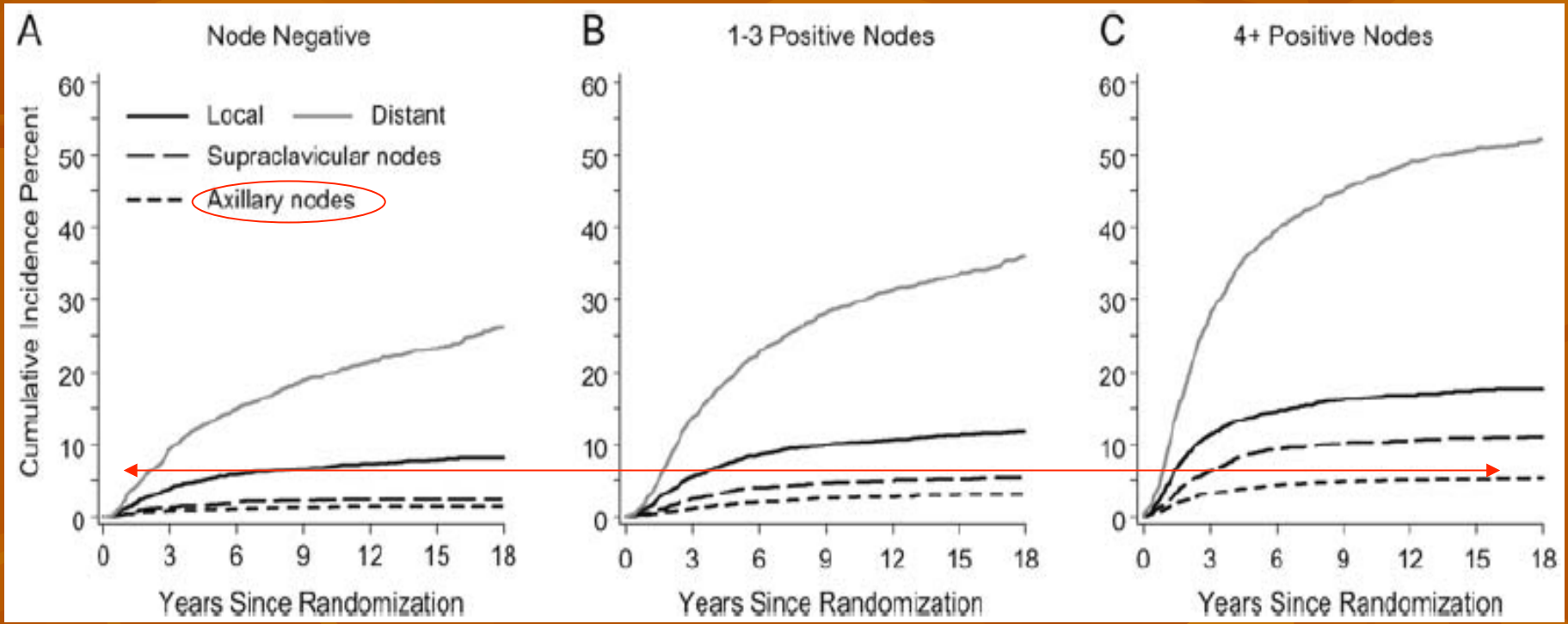
N+1-3 1,1%

N+ ≥4 1,3%

Gentilini O et al. Ann Oncol 2007, 18:1342-1347

Sites LRR and DM according to N status

13 IBCSG R Trials, 8106 pts RM



From Karlsson P et al. Ann Oncol 2012, 23:2852-2858, modified

Involved/examined nodes

- Nodal Ratio is correlated to risk LRR
- ≥ 20-25% (± age...)

Recht A et al 1999 JCO 17:1689-1700
Katz A et al. Int J Radiat Oncol Biol Phys 2001, 50:397-403
Truong PT et al. Int J Radiat Oncol Biol Phys 2007, 68:59-65

- Low uninvolved nodes → inadequate surgery or pathological understaging

Karlsson P et al. Ann Oncol 2012, 23:2852-2858

NUMBER OF POSITIVE/EXAMINED NODES
Axillary relapse

2016 ECOG pts no RT

examined nodes	pts	10 ys rate (%)	SE
N+ 1-3			
2-5	43	7	4.0
6-10	215	0.5	0.5
≥ 11	758	1,5	0.5
		p .0009	
N+ ≥ 4			
4-5	18	11,8	8.8
6-10	138	7.6	2.3
≥ 11	840	5,9	0.8
		p .63	

In N1 small n° examined nodes impacts on axillary R

Recht A et al 1999 JCO 17:1689-1700 modified

Bio-pathological factors

- Età <40-50 ys
- Tumor size
- Grading
- ER –
- LVI +
- Size nodal metastasis
- Biological subtype HER-2 + and basal

Risk factors for LRR

Truong PT et al. Int J Radiat Oncol Biol Phys 2005, 61:1337-1347
Wo JY et al. Int J Radiat Oncol Biol Phys 2010, 77:188-196
Karlsson P et al. Ann Oncol 2012, 23:2852-2858
Nielsen HM et al. Radiother Oncol 2006, 79:147-155
Grills IS et al. Int J Radiat Oncol Biol Phys 2003, 56:658-670

Ten-year cumulative incidence of axillary recurrence

Risk factor	No. (%) of patients	%Axilla (SE)
Nodes involved		
None	2555 (32)	1.3 (0.2)
1-3	3260 (40)	2.6 (0.3)
4-10	1744 (22)	4.9 (0.5)
≥11	547 (7)	4.9 (0.9)
Nodes uninvolved		
0-7	1925 (24)	5.2 (0.5)
8-11	1953 (24)	2.9 (0.4)
12-16	2126 (26)	2.2 (0.3)
≥17	2102 (26)	1.3 (0.2)
Nodes examined		
≤10	1940 (24)	3.8 (0.4)
11-14	2076 (26)	3.5 (0.4)
15-19	2053 (25)	2.2 (0.3)
≥20	2037 (25)	2.0 (0.3)

From Karlsson P et al. Ann Oncol 2012, 23:2852-2858, modified

Ten-year cumulative incidence of axillary recurrence

Risk factor	No. (%) of patients	%AR (SE)
Tumor size, cm		
≤2	3200 (39)	2.4 (0.3)
>2	4623 (57)	3.0 (0.3)
Unknown	283 (3)	5.2 (1.4)
Tumor grade		
1	1126 (14)	1.3 (0.4)
2	3520 (43)	2.6 (0.3)
3	3036 (37)	3.5 (0.3)
Unknown	424 (5)	3.8 (0.9)
Peritumoral vessel invasion		
No	3823 (47)	2.0 (0.2)
Yes	2754 (34)	3.8 (0.4)

From Karlsson P et al. Ann Oncol 2012, 23:2852-2858, modified

Ten-year cumulative incidence of axillary recurrence

Risk factor	No. (%) of patients	%AR (SE)
Age, years		
<40	949 (12)	5.1 (0.7)
40–49	2607 (32)	2.7 (0.3)
50–59	2452 (30)	2.4 (0.3)
≥60	2098 (26)	2.5 (0.3)
Estrogen receptor status		
Negative	2383 (29)	3.1 (0.4)
Positive	4760 (59)	2.5 (0.2)
Unknown	963 (12)	3.6 (0.6)

<40ys, N+ ≥4, <8 Uninvolved nodes →
10 ys axillary relapse rate about 5%

From Karlsson P et al. Ann Oncol 2012, 23:2852-2858, modified

Extracapsular extension
Indication for RT?

Author	Pts	BCS/RM	N tot	N +	Axillary R % ECE+	ECE-
Gruber G et al. Strhlenther Onkol 2005	254	BCS/RM	17	3	3	0
Gruber G et al. Annals Oncol 2008	933	BCS/RM	>11	N+	4.1	2.1 10ys
Stranzl H et al. Strahlent Onk 2004	301 ECE+	BCS/RM	>10	N+	0,7	
Mignano et al. Cancer 1999	487	RM	13	≥2	0	3

ECE+ N+ 1-3 → 10ys AR 3.2%
ECE+ N+ ≥ 4 → 10ys AR 4.9%

Gruber G et al. Ann Oncol2008, 19:1393-1401

Correlation ECE-N+, not prognostic factor
No indication for Axillary RT

Truong P. et al.CMAJ 2004, 170:1263-1273
Recht A. Houlihan MJ. Cancer 1995, 76:1491-1512

Level of axillary involvement
Indication for axillary RT?

- 549 pts RM 18 LN N+
- Level III, N+≥ 4, T3 → negative on LRRFS

Kuru B et al World J Surg 2004,28;236-241

- Involved level no independent prognostic factor for DFS e OS → Number N+

Barth RJ et al Arch Surg 1991, 126:574-577 no

Axillary apex involvement

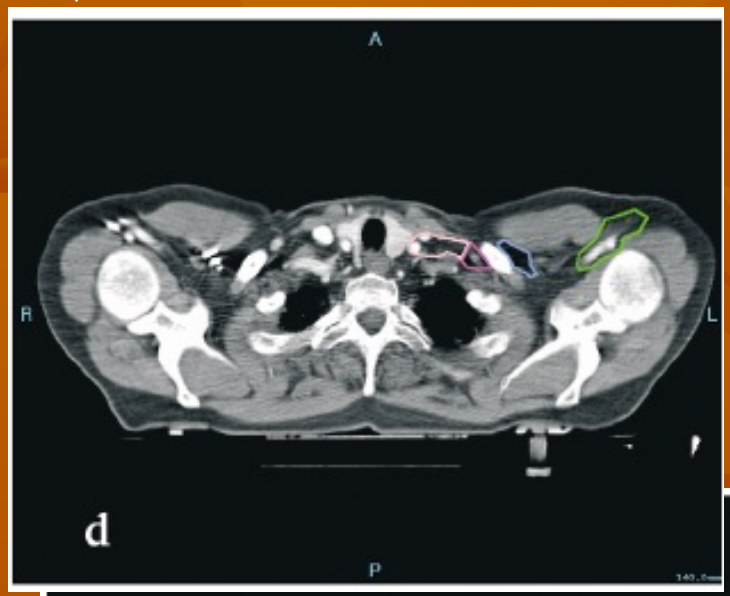
- Risk of involvement of III level N (medial to the border of pectoralis minor muscle) increases when lower level are involved and tumor size increases
- 1-2% false negative dissection Lev I-II

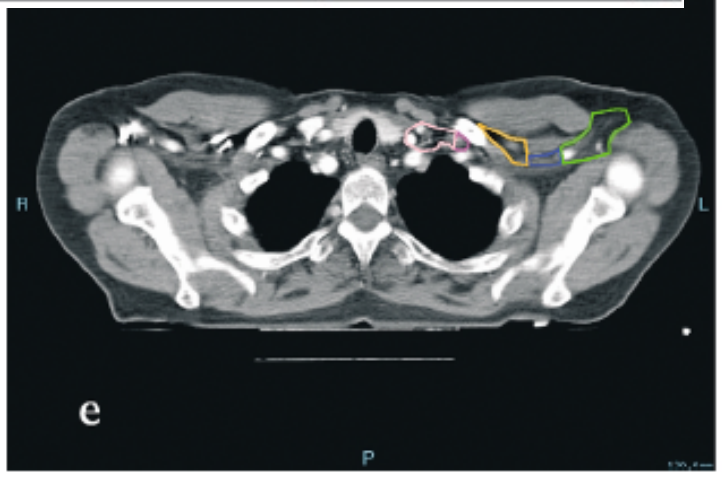
- "Supraclavicular" field should include supraclavicular, infraclavicular and axillary apical N

Recht A. et al. J Clin Oncol 2001, 19:1539-1569
Recht A., Houlihan MJ. Cancer 1995, 76:1491-1512
Truong P. et al.CMAJ 2004, 170:1263-1273
Grills IS et al. Int J Radiat Oncol Biol Phys 2003,56:658-670

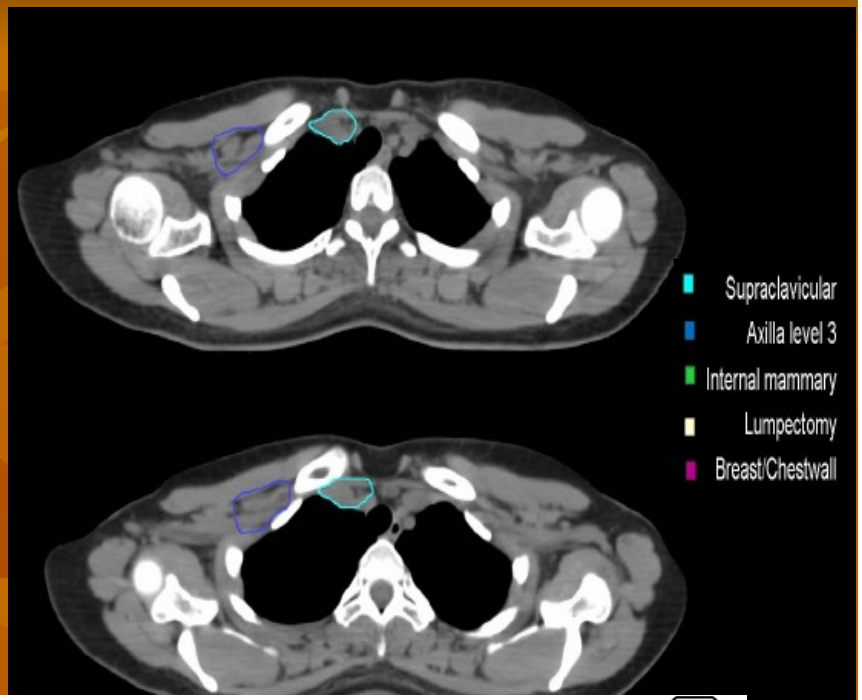
From Dijkema IM et al. Radiother Oncol 2004, 71:287-295, modified

Green: level I axillary LNs.
Dark blue: level II axillary LNs.
Orange: level III axillary LNs.
Pink: medial SC LNs. Purple: lateral SC LNs.
Light blue: ICLNs. Yellow: interpectoral LNs.
Turquoise: IMN.

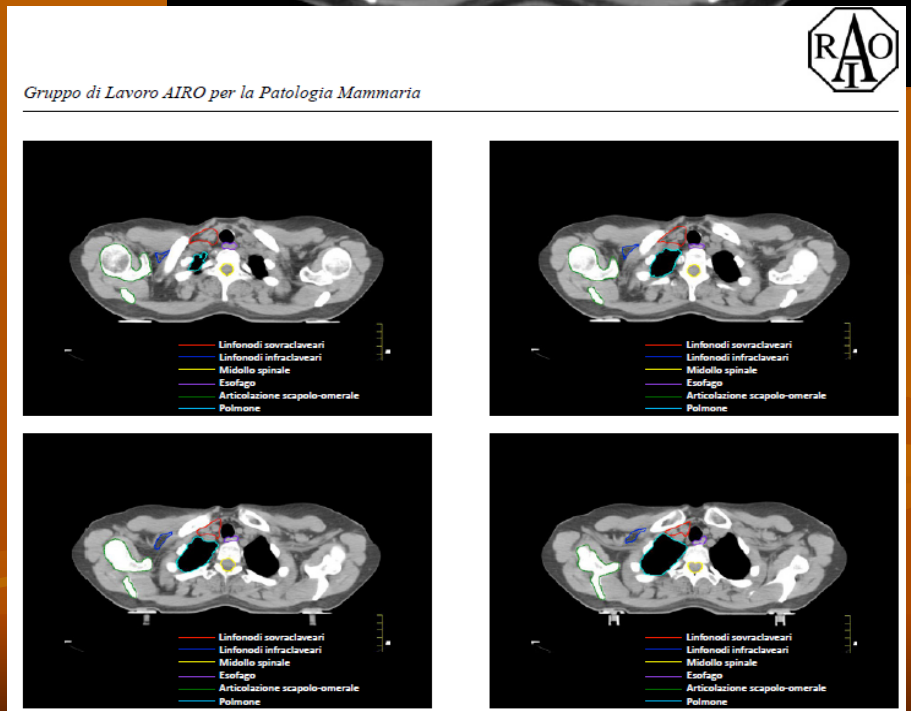




RTOG Atlas



AIRO 2013



Is axillary irradiation indicated after neoadjuvant chemotherapy?

- T3N0-N3
- LN removed 15-17
- ± RT post operative, no axillary RT

- Axillary relapse 1,2-1,8%
- No A RT after dissection

Wright JL et al. Cancer 2013, 119:16-25
Nagar H et al. Int J Radiat Oncol Biol Phys 2011, 81:782-787
Daveau C et al. Int J Radiat Oncol Biol Phys 2010, 78:337-342

Late Toxicity

- Extending RT volume increased risk of adverse effects
- lymphedema, pneumonitis, cardiac disease

- Wide Range rate lymphedema 6-90%
- No agreement on diagnostic method
- Assessement time

Hayes SC et al. Cancer 2012, 118:2237-2249
Truong P. et al.CMAJ 2004, 170:1263-1273
Recht A. Houlihan MJ. Cancer 1995, 76:1491-1512

Late Toxicity

Risk factor for lymphedema

- Number of dissected axillary nodes
- RT
- Body mass index
- Adjuvant chemotherapy

- Model to estimate risk

Surgery alone	→ Lymphedema 5-10%
Surgery/SC+A apex RT	→ Lymphedema 5-12,5%
Surgery/full A RT	→ Lymphedema 9-36%

Overgaard M et al. N Engl J Med 1997, 337:949-955
RagazJ et al. N Engl J Med 1997, 337:956-962
Truong P. et al.CMAJ 2004, 170:1263-1273
Recht A. Houlihan MJ. Cancer 1995, 76:1491-1512
Myungsoo Kim et al. Int J Radiat Oncol Biol Phys 2013, 86:498-503
Kwan W et al. J Clin Oncol 2002, 20:4242-4248

Spanish Consensus on the regional lymph nodes irradiation

Consensus on Axillary nodes irradiation

≥ 4 N+ sufficient lymphoadenectomy

SC N + axillary level III

RT axilla if

1) extensive axillary fat involvement
2) Size nodes >4 cm
3) >75% metastatic nodes
4) Residual disease

Bayo E et al. Clin Transl Oncol 2013

DEGRO Guidelines axillary RT after dissection

- Presence of residual tumor in the axilla
- Clinical tumor spread in the axilla after incomplete axillary dissection
- No sufficient data supporting irradiation of the axilla in case of extracapsular spread

Sautter-Bihl ML et al. Strahlent Onkol 2008, 184:347-353

Radiotherapy after axillary dissection: When? Conclusion

- ✓ Low risk AR after dissection I-II Lev ~ 0-3%
- ✓ High risk pts → RT SC, IC, axillary apex
  Lymphedema ~ 10%
- ✓ Increased risk side effects >10% whith surgery + full A RT

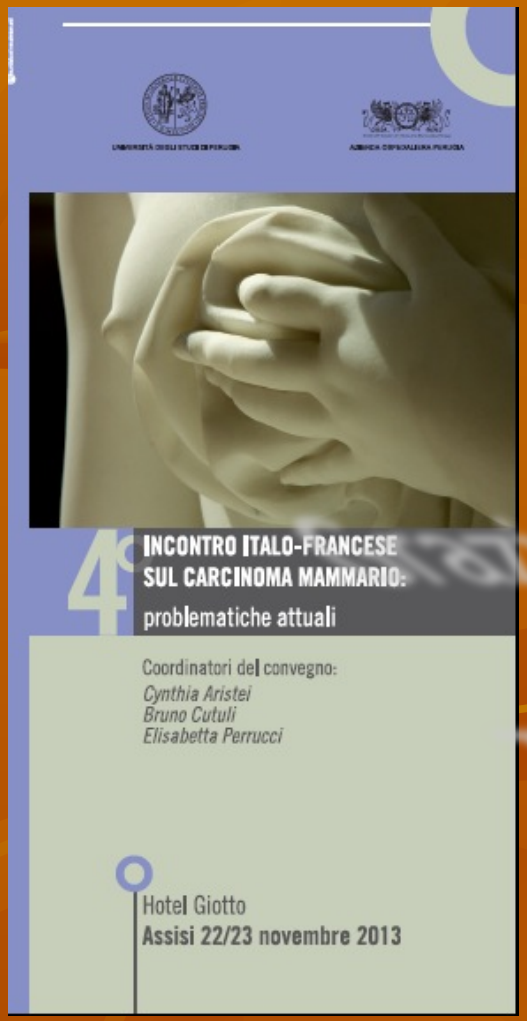
Truong P. et al. CMAJ 2004, 170:1263-1273
Recht A., Houlihan MJ. Cancer 1995, 76:1491-1512
Katz A et al. J Clin Oncol 2000, 18:2817-2827
Recht A. et al. J Clin Oncol 2001, 19:1539-1569

Radiotherapy after axillary dissection:When?
Conclusion

- No axillary RT …non indicata dopo dissezione indipendentemente da n° LN + e/o ECE+…
- …a meno che non ci sia la presenza accertata di malattia residua
- o un fondato sospetto …

High Nodal Ratio/low uninvolved nodes, young patient, nodal size, LVI …

AIRO La Radioterapia dei Tumori della Mammella Indicazioni e Criteri Guida, 2013



Grazie dell'attenzione

Thanks for your attention