



Mudando paradigmas em radioterapia e manejo da axila

Guidelines de radioterapia pós mastectomia

Fernando Obst

GBECAM 2018

CONFLITOS DE INTERESSE



POSTMASTECTOMY RT (PMRT)

- Dois potenciais benefícios:
 - Diminuir taxa de recorrência local
 - Aumentar SV global e câncer específica
- Magnitude do benefício de PMRT depende do risco basal para recorrência

Clarke M. Lancet 2005

Danish Breast Cancer Cooperative Group. JCO 2006

Ragaz J. J Natl Cancer Inst 2005



POSTMASTECTOMY RT (PMRT)

EBCTCG 2005 meta análise

- 8.500 ptes mastectomia c / EA N+
- Incluídas em trials de RT
- RT (geralmente parede torácica + LNs regionais) Vs No RT
- Menor recorrência local (7.8% Vs 29% No RT)
- Melhor SV cancer específica (60.1% Vs 54.7% No RT)



POSTMASTECTOMY RT (PMRT)

EBCTCG 2014 meta análise

- 8135 women randomly assigned to treatment groups during 1964-86 in 22 trials of radiotherapy to the chest wall and regional lymph nodes after mastectomy and axillary surgery versus the same surgery but no radiotherapy.
- Follow-up lasted 10 years for recurrence and to Jan 1, 2009, for mortality.
- 3786 women had axillary dissection to at least level II and zero, one to three, or four or more positive nodes.
- All were in trials in which radiotherapy included the chest wall, supraclavicular or axillary fossa (or both), and internal mammary chain.
- After mastectomy and axillary dissection, radiotherapy reduced both recurrence and breast cancer mortality in the women with one to three positive lymph nodes in these trials even when systemic therapy was given.



POSTMASTECTOMY RT (PMRT) - PLANEJAMENTO

- Parede torácica e linfonodos (LNs) regionais (supra e infra claviculares)
- Inclusão da axila (exceto em pacientes c/ completo esvaziamento axilar - EA)
- Inclusão cadeia MI: individualizar
- Completo EA: PMRT campos limitados
- Risco de linfedema pós EA c/PMRT:
 - 40% campo axilar
 - 3% campos supra/infraclaviculares



POSTMASTECTOMY RT (PMRT)

Guidelines



Postmastectomy Radiotherapy: An American Society of Clinical Oncology, American Society for Radiation Oncology, and Society of Surgical Oncology Focused Guideline Update

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San Antonio Breast Cancer Symposium, December 5-9, 2017

Postmastectomy Radiotherapy: An American Society of Clinical Oncology, American Society for Radiation Oncology, and Society of Surgical Oncology Focused Guideline Update

**Recht A, Comen EA, Fine RE, Fleming GF, Hardenbergh PH, Ho AY, Hudis CA, Hwang ES, Kirshner JJ, Morrow M, Salerno KE, Sledge GW Jr, Solin LJ, Spears PA, Whelan TJ, Somerfield MR, Edge SB
J Clin Oncol 34:4431-4442, 2016**

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ASCO-ASTRO-SSO 2016 PMRT GUIDELINE PT1-2N1

- Revisão sistemática da literatura
- ASCO Guideline PMRT 2001
- Joint Panel (update em colaboração c/ ASTRO e SSO)
- Foco em áreas controversas



ASCO-ASTRO-SSO 2016 PMRT GUIDELINE

Question 1: Is PMRT indicated in patients with T1-2 tumors with one to three positive axillary lymph nodes who undergo ALND?

Question 2: Is PMRT indicated in patients with T1-2 tumors and a positive SNB who do not undergo completion ALND?

Question 3: Is PMRT indicated in patients presenting with clinical stage I or II cancers who have received NAST?

Question 4: Should RNI include the internal mammary (IMNs) and/or supraclavicular-axillary apical nodes when PMRT is used in patients with T1-2 tumors with one to three positive axillary nodes?



ASCO-ASTRO-SSO 2016 PMRT GUIDELINE

Question 1: Is PMRT indicated in patients with T1-2 tumors with one to three positive axillary lymph nodes who undergo ALND?



ASCO-ASTRO-SSO 2016 PMRT GUIDELINE

Question 1: Is PMRT indicated in patients with T1-2 tumors with one to three positive axillary lymph nodes who undergo ALND?

Updated recommendations: 1a

Painel unânime: PMRT reduz risco de falha locoregional (qualquer recorrência) e mortalidade cancer específica em pacientes pT1-2pN1 (1-3 LNs+).

(type: evidence based; evidence quality: high; strength of recommendation: strong).



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PT1-2N1

- P/ alguns subgrupos de baixo risco de falha local: benefício absoluto de PMRT superado pela potencial toxicidade.
- Razão “Benefício/Toxicidade” variável.
- Recomendação de PMRT: julgamento clínico, de modo multidisciplinar e ASAP.



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PT1-2N1 – CÁLCULO DO BENEFÍCIO

- **Características de **pacientes** de menor benefício de PMRT:**
 - Idade > 40-45a
 - Expectativa de vida limitada (idade ou comorbidades)
 - Condições coexistentes que aumentem risco de complicações
- **Achados **patológicos** associados a baixa carga tumoral:**
 - T1
 - no LVI
 - LN + único e/ou pequeno tamanho mets nodal (cutt-off MSKCC ≤ 2 mm / MDACC ≤ 10 mm)
- **Características **biológicas** da doença associados a melhores resultados e SV e/ou maior efetividade da terapia sistêmica**
 - Tumor de baixo grau
 - Receptor hormonal forte+



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PT1-2N1 - CÁLCULO DO BENEFÍCIO

- Vários modelos adaptados ao risco p/ cálculo do benefício de PMRT e p/ dividir tomada de decisão c/ pacientes.
- PAINEL: evidência insuficiente p/ endossar qq modelo específico que indubitavelmente possa definir específicos subgrupos de pacientes em que PMRT não deva ser empregada.



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Question 2: Is PMRT indicated in patients with T1-2 tumors and a positive SNB who do not undergo completion ALND?



ASCO-ASTRO-SSO 2016 PMRT GUIDELINE

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- P/ ptes T1-2 N-, BLS geralmente empregada na mastectomia, com omissão da ALND se LNs negativos. ALND geralmente empregada se LNs+, mas há controversia se sempre necessária, especialmente se doença limitada comprometendo LNs.
- Painel reconhece que parte dos cirurgiões omitem ALND c/ 1-2 LN sentinela positivos (extrapolação dos trials randomizados de BCS e WBI).
- Recomendação: em casos de omissão da ALND por escolha do cirurgião e paciente, painel recomenda PMRT somente se a indicação não necessitar de informação adicional da axila.
(type: informal consensus; evidence quality: weak; strength of recommendation: moderate).



ASCO-ASTRO-SSO 2016 PMRT Guideline: pT1-2N1 - After Positive Sentinel Node Biopsy

- **“Would I recommend PMRT for this patient if she had undergone simultaneous ALND and there were no additional nodal metastases in the nonsentinel nodes?”**
- **If the answer is "no", then ALND should be performed.**
- **This discussion should ideally be had prior to surgery.**

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Question 2: Is PMRT indicated in patients with T1-2 tumors and a positive SNB who do not undergo completion ALND?

- PMRT se cirurgia menor (BLS) e se substancial chance de adicionais LNs não sentinela positivos.
- Parcela de cirurgiões questionam necessidade de ALND considerando trials randomizados ACOSOG Z0011 e AMAROS.



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Question 3: Is PMRT indicated in patients presenting with clinical stage I or II cancers who have received NAST?



ASCO-ASTRO-SSO 2016 PMRT GUIDELINE

Question 3: Is PMRT indicated in patients presenting with clinical stage I or II cancers who have received NAST?

Updated recommendation

- Pacientes que persistem N+ após NAST (< RC) devem receber PMRT.
- Dados observacionais sugerem baixo risco de recorrência locorregional em pacientes clinicamente N0 e recebem NAST.
- Evidência ainda insuficiente se PMRT deve ser empregada ou pode ser omitida neste grupo.
- Painel recomenda inclusão de pacientes em clinical trials que examinem esta questão.
(type: informal consensus; evidence quality: low; strength of recommendation: weak).



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Question 3: Is PMRT indicated in patients presenting with clinical stage I or II cancers who have received NAST?

Estudos em andamento de NAST

NRG 9353

ALLIANCE A011202



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Question 4: Should RNI include the internal mammary (IMNs) and/or supraclavicular-axillary apical nodes when PMRT is used in patients with T1-2 tumors with one to three positive axillary nodes?



ASCO-ASTRO-SSO 2016 PMRT GUIDELINE

Question 4: Should RNI include the internal mammary (IMNs) and/or supraclavicular-axillary apical nodes when PMRT is used in patients with T1-2 tumors with one to three positive axillary nodes?

- Volume mínimo mandatório de PMRT de consenso no painel: parede torácica + supraclavicular-axilar apical LNs.
- Permanecem controvérsias quanto à inclusão deliberada de cadeia MI e axila níveis I e II.
- Cobertura linfonodal de 20/22 trials da EBCTCG metanálise mostram benefício de PMRT c/ inclusão de cadeia mamária interna (inclusão não uniforme).



ASCO-ASTRO-SSO 2016 PMRT GUIDELINE

Question 4: Should RNI include the internal mammary (IMNs) and/or supraclavicular-axillary apical nodes when PMRT is used in patients with T1-2 tumors with one to three positive axillary nodes?

Updated recommendation

- Painel recomenda tratamento geralmente administrado a ambas cadeia mamária interna e supraclavicular e axilar apical (além da parede torácica ou mama reconstruída) quando PMRT indicada para pacientes LNs+.
- Subgrupos de limitado (se algum) benefício em receberem RT de todas as cadeias comparados com tratamento de LNs regionais somente ou talvez somente parede torácica ou mama reconstruída. Evidência insuficiente p/ definir tais grupos, além de considerações quanto à toxicidade cardíaca e pulmonar, mesmo com melhor técnica.

(type: informal consensus; evidence quality: intermediate; strength of recommendation: moderate).



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RECOMENDAÇÕES

- N+ associado a > risco de recorrência local (em geral favorece PMRT)
- Magnitude do benefício de PMRT e força de recomendação depende do número de LNs+.
- >3 PMRT parede torácica e LNs regionais (supra e infraclaviculares)
- 1-3 alvo de debate (geralmente empregar PMRT em ordem de maximizar oportunidade de reduzir recorrência local e potencialmente melhorar SV cancer-específica).
- outros fatores: margens +, T2N- c/ fatores alto risco (alto grau, triplo-, idade jovem, LVI)



ASCO-ASTRO-SSO 2016 PMRT GUIDELINE

RECOMENDAÇÕES

- Nem todas as pacientes tratadas com atuais dissecações axilares e modernas terapias sistêmicas se beneficiarão de PMRT p/ justificar seu uso.
- Embora a morbidade por PMRT tenha diminuído com incremento de tecnologia (técnicas e planejamento) comparado com a RT dos trials incluídos nas metanálises EBCTCG, ela não é negligenciável.
- Doença cardíaca e câncer radioinduzido podem levar décadas p/ aparecer, possivelmente mesmo com melhor técnica.
- RT regional pode aumentar linfedema, especialmente pacientes submetidas a ALND.
- Número crescente de pacientes submetidas a cirurgia de reconstrução. PMRT pode piorar resultados cosméticos (complicações a curto e longo prazo).
- Portanto, se possível for determinar que o risco de recorrência local seja baixo em certos subgrupos, considerar não recomendar PMRT em tais pacientes.

Whelan TJ. NEJM 2015
Warren LE. IJROBP 2014
Kelley BP. Ann Surg Oncol 2014
Momoh AO. Ann Surg Oncol 2014









Clinical Investigation

Outcomes of Post Mastectomy Radiation Therapy in Patients Receiving Axillary Lymph Node Dissection After Positive Sentinel Lymph Node Biopsy



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Received Mar 7, 2016, and in revised form Jun 8, 2016. Accepted for publication Jul 1, 2016.



ASTRO'S 59TH ANNUAL MEETING

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Post-mastectomy radiotherapy for node-negative breast
cancer with tumor size of five centimeters or more:
A Meta-analysis

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Purpose

- The benefit of Post-Mastectomy Radiotherapy (PMRT) for pT3 node-negative breast cancer has been questioned.
- We conducted a meta-analysis of prospective and case-control series to investigate the loco-regional recurrence (LRR) benefit of PMRT in node negative breast cancer with tumor size ≥ 5.0 cm.



Conclusion

- LRR is significantly decreased with PMRT in node-negative patients with tumor size $\geq 5\text{cm}$.
- This benefit was evident in both the subgroups who underwent Axillary Sampling as well as Axillary Dissection.
- These results should inform clinical decision making when considering addition of post-mastectomy radiation in patients with tumors size $\geq 5\text{cm}$.
- Individualized decision making is recommended based on patient specific clinicopathologic features; a discussion of PMRT should be initiated in patients with tumors of 5cm or greater.





Single Stage Permanent Implant Reconstruction Has Better Outcome Than Tissue Expander/Implant in Patients Treated with Post-mastectomy Radiation

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Objective and Design

- We sought to identify which type of implant-based reconstruction has the most favorable outcome in the setting of post-mastectomy radiation therapy (PMRT).
- We conducted a retrospective cohort study of **1179** breast cancer patients who underwent a total of **1729** mastectomies, all treated at one institution from 1997-2014.

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Study Design

- Reconstructed breasts were dichotomized to either PMRT (study group) or no-PMRT (control group)
- PMRT group included **501** mastectomies
- No- PMRT group included **1228** mastectomies
- The overall cohort included: **1196** therapeutic mastectomies and **533** prophylactic mastectomies

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Post-mastectomy Radiation Therapy

- PMRT was delivered using opposed- tangent photon beams to median total chest wall dose of 50 Gy over 5-6 weeks at 1.8 – 2 Gy per fraction.
- 61% of mastectomies had an *en-face* electron boost (median 10Gy)
- 81% of PMRT cases had regional lymph node radiation (RLNR)

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Definitions of reconstruction failure (RF) as an outcome variable

Implant-based Reconstruction Failure

- **Overall RF**

Tissue expander (TE) or permanent implant (PI) removal due to complications requiring surgical intervention regardless of further attempts to replace the TE or PI.

- **Absolute RF**

TE or PI removal with failure to replace the implant, with or without conversion to autologous tissue graft.

- **Salvaged RF**

TE or PI removal due to complications with successful attempt(s) at re-reconstruction with either TE/I or PI

Autologous Tissue Reconstruction Failure

- The development of complications that required immediate surgical intervention.



Cumulative Incidence of Overall RF



	TE/I	DTI	P-Value
PMRT	33.8%	16.4%	$p=0.0007$
No PMRT	13.9%	8.4%	$p=0.074$

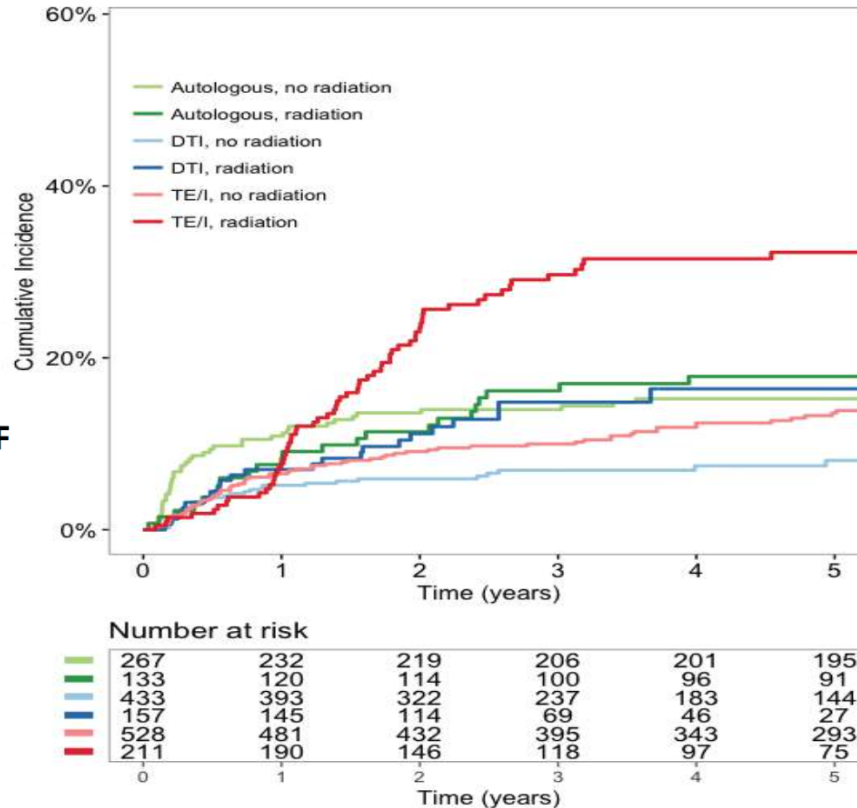
PMRT:

TE/I had higher 5-year CI of overall RF ($p=0.0007$).

No PMRT:

5-year CI of overall RF was not significantly different between TE/I and DTI ($p=0.074$).

Kaplan-Meier Plot



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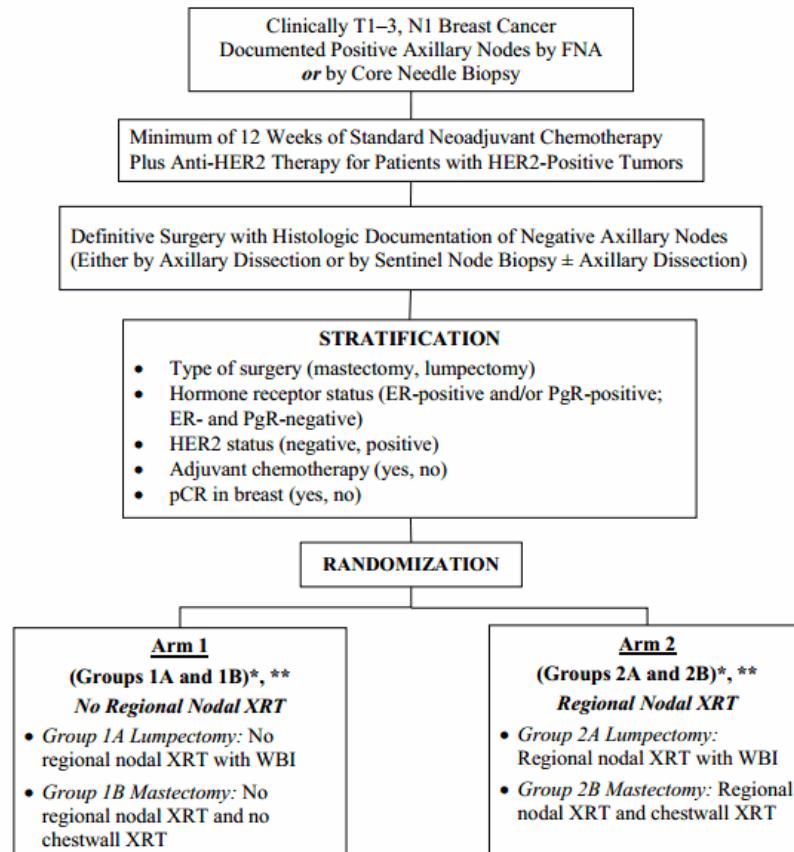
Conclusion

- In the setting of PMRT, single- stage Direct- to- implant breast reconstruction (DTI) has **significantly lower rate of overall RF** compared to two-stage tissue expander/implant (TE/I) (**16.4% vs 33.8% ; respectively; $p=0.0007$**)
- The 5- year complication rate was not significantly different between irradiated ATR and irradiated single stage (DTI) (18.2% vs 16.4%; respectively; $p=0.99$)
- **Single stage DTI could be considered a preferable alternative to Two stage TE/I in select group of patients, when PMRT is indicated.**



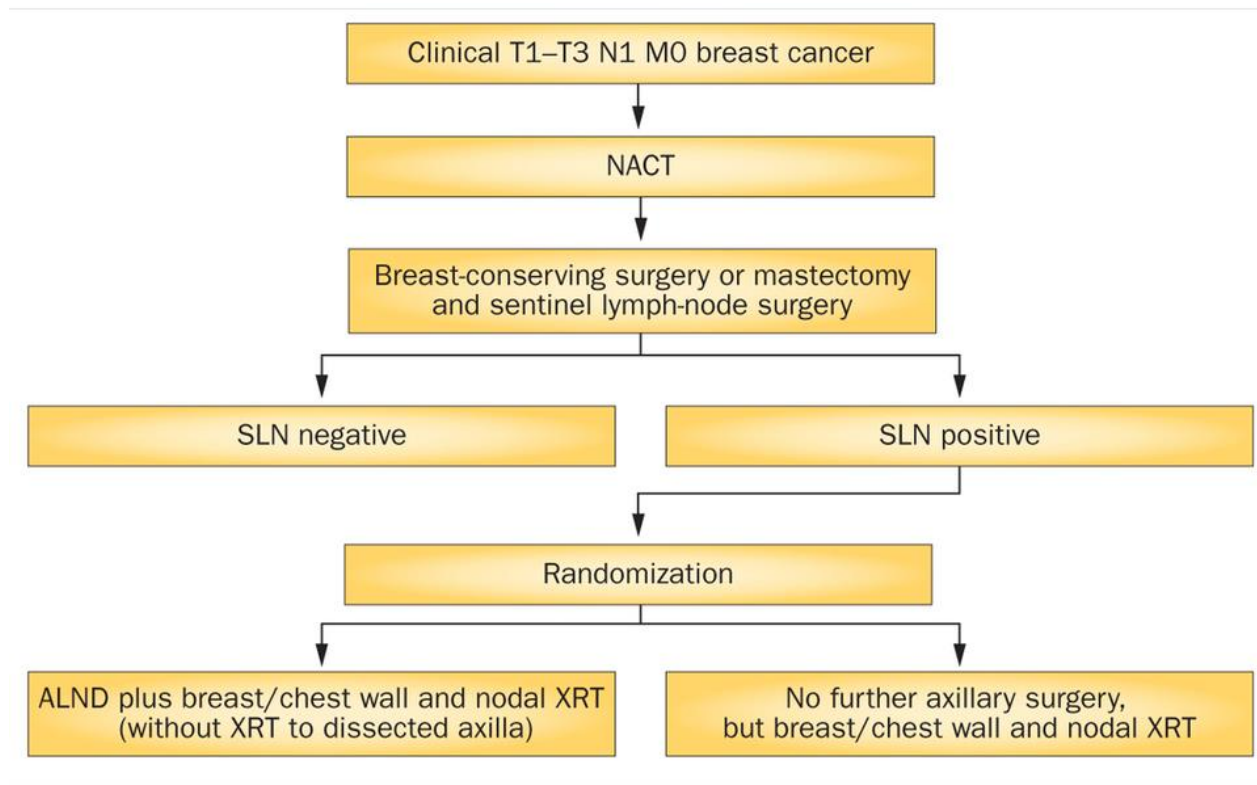
NSABP B-51/RTOG 1304

YPN0



ALLIANCE A11202

YPN+(SN)



○ NSABP B-51

Estimated Enrollment: 1636
Study Start Date: August 2013
Estimated Study Completion Date: August 2028
Estimated Primary Completion Date: July 2023 (Final data collection date for primary outcome measure)

○ ALLIANCE A11202

Estimated Enrollment: 2918
Study Start Date: February 2014
Estimated Primary Completion Date: January 2024 (Final data collection date for primary outcome measure)

