Recommended Proton Therapy Indications

National Association of Proton Therapy (NAPT) member medical directors under the leadership of William Hartsell, MD, Robert Foote, MD, and Nancy Mendenhall, MD developed this document summarizing recommended proton beam therapy indications by tumor site. NAPT is a non-profit organization promoting education and public awareness of the clinical benefits of proton beam radiation therapy for cancer treatment. More information on NAPT is available on its website (www.proton-therapy.org).

1. **Breast Cancer**

2. **Esophagus Cancer**

3. **Gastrointestinal (GI) Cancer**

4. **Hematologic Cancer**

5. **Prostate Cancer**

6. **Thoracic Cancer**

Breast Cancer
Recommended Proton Therapy Indications

Indications:

- **Left or Right-sided early or locoregionally advanced breast cancer requiring breast or chest wall plus regional nodal irradiation** (i.e. lymph node positive disease, advanced T stage and/or medial tumor location)

  - Adjuvant radiotherapy improves survival in breast cancer patients, suggesting that persistence of locoregional tumor is associated with an increased risk of developing metastases and death.[1,2]. Results of modern randomized controlled clinical trials highlight the importance of regional nodal irradiation in reducing distant events in this population.[3-7] Targeting of the regional lymphatics results in lung and heart doses associated with increased major cardiac events, cardiac deaths, lung cancer, and lung cancer deaths in a patient population where advances in systemic therapy and other multidisciplinary care has resulted in decreasing breast cancer specific mortality.[8-10] Proton radiotherapy improves coverage of the regional lymphatics while substantially reducing mean lung and mean heart doses to levels significantly correlated with reduced cardiac events, lung cancer, and symptomatic pneumonitis.[11-15]

  - **Inclusion criteria:**
    - Age ≥ 18 years
    - Histologic confirmation of breast cancer
    - Lumpectomy or mastectomy with or without immediate reconstruction
    - The axilla must be staged by sentinel node biopsy alone, sentinel node biopsy followed by axillary node dissection, or axillary lymph node dissection alone
    - Whole breast/chest wall and regional nodal irradiation indicated (lymph node positive disease, T3-T4, medial tumor location) .
    - pStage T1-T4N0-N3M0 or ypStage T0-4N0-N3M0
    - Breast implants and expanders allowed
    - Improved target coverage for regional nodes or absolute difference in mean heart dose between proton and photon plans (with photon cardiac sparing technique such as breath hold, IMRT, or prone positioning) >1.35 Gy or absolute difference in ipsilateral lung volume receiving 20 Gy between proton and photon plans >10%

  - **Exclusion criteria:**
    - Medical contraindication to receipt of radiotherapy.
    - Severe active co-morbid systemic illnesses or other severe concurrent disease which, in the judgment of the physician, would contraindicate any radiation therapy.
    - Active systemic lupus or scleroderma.

- o Pregnancy or women of childbearing potential who are sexually active and not willing/able to use medically acceptable **forms of contracepti**on

- **Early stage Breast cancer with indications for whole breast radiotherapy**
  - Darby et al. have established that rates of coronary events increase linearly with mean dose to the heart by 7.4% per gray with no apparent threshold.[6] The increase begins within a few years after exposure, and continues for at least 20 years. Proton whole breast radiotherapy achieves mean heart doses below <0.5Gy. Best evidence suggests proton radiotherapy is associated with a clinically significant >10% reduction in the rate of major coronary events in patients determined to have a >1.35Gy improvement in mean heart dose with proton, compared with photon planning.[8-10]

  - **Inclusion criteria:**
    - o Female
    - o Age ≥ 18 years.
    - o Histological confirmation of breast cancer
    - o Lumpectomy
    - o For invasive breast cancer the axilla must be staged by sentinel node biopsy alone, sentinel node biopsy followed by axillary node dissection, or axillary lymph node dissection alone
    - o pStage T0-T3N0-N1M0 or ypStage T0-T3N0-N1micM0
    - o Whole breast irradiation with or without a lumpectomy cavity boost indicated
    - o Absolute difference in mean heart dose between proton and photon plans (with photon cardiac sparing technique such as breath hold, IMRT, or prone positioning) >1.35 Gy or absolute difference in ipsilateral lung volume receiving 20 Gy between proton and photon plans >10%
  - **Exclusion criteria:**
    - o Medical contraindication to receipt of radiotherapy.
    - o Sever**e** active co-morbid **s**ystemic illnesses or other severe concurrent disease which, in the judgment of the physician, would contraindicate any radiation therapy.
    - o Active systemic lupus or scleroderma.
    - o Pregnancy or women of childbearing potential who are sexually active and not willing/able to use medically acceptable forms of contraception

- **Left and Right-sided early stage (invasive and non-invasive) Breast cancer** with clinical indications for partial breast irradiation as described below
  - The safety and efficacy of proton partial breast irradiation is established for early stage breast cancer.[13] Proton PBI provides a more homogeneous dose distribution and reduction in exposure to the normal breast, heart, and lung

compared with photon and brachytherapy PBI techniques and has been associated with excellent local control and reduced toxicity.[17-20]

- **Inclusion criteria:**
    - Female
    - Age ≥ 50 years at diagnosis
    - Grade 1-3 invasive ductal, mucinous, tubular, colloidal, or pure ductal carcinoma in situ (DCIS) measuring ≤ 2cm (clinical stage T1).
    - Estrogen Receptor (ER)+ (ER- DCIS meeting other eligibility criteria are eligible)
    - Unicentric: Patients with microscopic multifocality are eligible as long as the total pathologic tumor size is <2cm.
    - Surgical treatment of the breast must have been lumpectomy.
    - The final margins of the resected specimen must be histologically free of tumor.
    - Pathologically node negative
    - Note: For patients with T1a, T1b, T1c invasive breast cancer (except T1mi), an axillary staging procedure should be performed (either sentinel lymph node biopsy alone or axillary dissection and the axillary node must be pathologically negative). Patients with N0 (i+) tumors on sentinel lymph node mapping or dissection (i.e., if the tumor deposit is 0.2mm or less as determined by immunohistochemistry or hematoxylin and eosin staining) will also be eligible.
    - Absolute difference in mean heart dose between proton and photon plans (with photon cardiac sparing technique such as breath hold, IMRT, or prone positioning) >1.35 Gy or absolute difference in ipsilateral lung volume receiving 20 Gy between proton and photon plans >10%

- **Exclusion criteria:**
    - Any of the following because of the risk of genotoxic, mutagenic and teratogenic effects:
        - Pregnant women
        - Nursing women
        - Women of childbearing potential who are unwilling to employ adequate contraception
    - Neoadjuvant chemotherapy
    - Prior history of ipsilateral breast cancer
    - Prior radiation therapy to the ipsilateral breast or thorax
    - Co-morbid systemic illnesses or other severe concurrent disease which, in the judgment of the physician, would make the patient inappropriate for proton therapy

- o Active collagen-vascular disease that, in the opinion of the treating physician, would make proton therapy hazardous for the patient
- o Paget's disease of the breast
- o Proven multicentric carcinoma (DCIS or invasive) in more than one quadrant or separated by 4 or more centimeters or diffuse (>1 quadrant) suspicious calcifications
- o Histologic evidence of angiolympatic invasion (ALI). Note: Cases termed focally suspicious for ALI but where no definitive ALI is found are eligible.
- o Surgical margins that cannot be microscopically assessed or that are positive
- o Pathologic tumor >2cm in size
- o Metastatic disease
- o Invasive lobular carcinoma or lobular carcinoma in situ
- o BRCA1 or BRCA2 mutation
- o Breast implants (patients who have had implants removed are eligible).
- o Extensive intraductal component
- o Active connective tissue disease
- o Reduction mammoplasty if 3DCRT or proton APBI are planned

Scientific Evidence:

1. Ebctcg Early Breast Cancer Trialists' Collaborative Group. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. *Lancet.* Mar 19 2014.
2. Darby S, McGale P, Correa C, et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. *Lancet.* Nov 12 2011;378(9804):1707-1716.
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5. Overgaard M, Hansen PS, Overgaard J, Rose C, Andersson M, Bach F, Kjaer M, Gadeberg CC, Mouridsen HT, Jensen MB, Zedeler K. Postoperative radiotherapy in high-ris premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b Trial. N Engl J Med 1997; 237 (14): 949-55.
6. Whelan TJ, Olivotto I, Ackerman I, Chapman JW, Chua B, Nabid A, Vallis KA, White JR, Rousseau P, Fortin A, Pierce LJ, Manchul L, Craighead P, Nolan MC, Bowen J, McCready DR, Pritchard KI, Levine MN, Parulekar W. NCIC-CTG MA.20: An

intergroup trial of regional nodal irradiation in early breast cancer [abstract]. J Clin Oncol. 2011;29(18 suppl):LBA1003.

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10. Clarke M, Collins R, Darby S, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet.* Dec 17 2005;366(9503):2087-2106.

11. Ares C, Khan S, Macartain AM, Heuerger J, Goitein G, Gruber G, Lutters G, Hug EB, Bodis S, Lomas AJ. Postoperative proton radiotherapy for localized and locoregional breast cancer: potential for clinically relelvant improvements? Int J Radiat Oncol Biol Phys. 2010. 76(3): 685-97.

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14. Xu N, Ho MW, Li Z, Morris CG, Mendenhall NP. Can proton therapy improve the therapeutic ratio in breast cancer patients at risk for nodal disease? Am J Clin Oncol 2014. 37(6): 568-74.

15. Depauw N, Batin E, Daartz J, et al. A novel approach to postmastectomy radiation therapy using scanned proton beams. *Int J Radiat Oncol Biol Phys.* Feb 1 2015;91(2):427-434.

16. Johansson J, Isacsson U, Lindman H, Montelius A, Glimelius B. Node-positive left-sided breast cancer patients after breast-conserving surgery: potential outcomes of radiotherapy modalities and techniques. *Radiother Oncol.* Nov 2002;65(2):89-98.

17. Bush DA, Do S, Lum S, et al. Partial breast radiation therapy with proton beam: 5-year results with cosmetic outcomes. *Int J Radiat Oncol Biol Phys.* Nov 1 2014;90(3):501-505.

18. Haviland JS, Owen JR, Dewar JA, et al. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. *Lancet Oncol.* Oct 2013;14(11):1086-1094

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Esophagus Cancer
Recommended Proton Therapy Indications

Indications:
1) **Adenocarcinoma or Squamous Cell Carcinoma** of proximal, middle, or lower esophagus or gastroesophageal junction

Inclusion criteria:
- Clinical stage T1-4 N0-3 M0

- Treatment intent is curative

- ECOG performance status 0-2

- Receiving high dose (≥ 40 Gy) definitive or neoadjuvant radiotherapy

- Receiving concurrent chemotherapy

- Dose-volume parameters for photon RT predict for ≥ 20% absolute risk of cardiac or pulmonary toxicity when the following cannot be met.

    - Lung mean dose ≤ 7 Gy or V5 ≤ 60%

    - V5 <1500 CC (Volume of total lung exposed to less than 5 Gy)

    - Heart mean dose ≤ 26 Gy, V30 < 46% (with no surgery)

    - V50<20% (Shirai, 2011)

    - The threshold parameters for considering proton therapy based on mean heart dose should be reduced if trimodality (including surgery) is used, although precise parameters are not clear at this point.

Exclusion criteria:
- Clinical stage Tx, Nx, M1

- Treatment intent is palliative

- Total radiotherapy dose is < 40 Gy

Scientific Evidence:
1. Ling TC, Slater JM, Nookala P, Mifflin R, Grove R, Ly AM, Patyal B, Slater JD, Yang GY. Analysis of Intensity-Modulated Radiation Therapy (IMRT), Proton and 3D Conformal Radiotherapy (3D-CRT) for Reducing Perioperative Cardiopulmonary Complications in Esophageal Cancer Patients. Cancers (Basel). 2014 Dec 5;6(4):2356-68. doi: 10.3390/cancers6042356. PMID: 25489937
2. Wang J, Wei C, Tucker SL, Myles B, Palmer M, Hofstetter WL, Swisher SG, Ajani JA, Cox JD, Komaki R, Liao Z, Lin SH. Predictors of postoperative complications after trimodality therapy for esophageal cancer. Int J Radiat Oncol Biol Phys. 2013 Aug 1;86(5):885-91. doi: 10.1016/j.ijrobp.2013.04.006. PMID: 23845841

3. Lin SH, Komaki R, Liao Z, Wei C, Myles B, Guo X, Palmer M, Mohan R, Swisher SG, Hofstetter WL, Ajani JA, Cox JD. Proton beam therapy and concurrent chemotherapy for esophageal cancer. Int J Radiat Oncol Biol Phys. 2012 Jul 1;83(3):e345-51. doi: 10.1016/j.ijrobp.2012.01.003. Epub 2012 Mar 13. PMID: 22417808

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5. Welsh J, Gomez D, Palmer MB, Riley BA, Mayankkumar AV, Komaki R, Dong L, Zhu XR, Likhacheva A, Liao Z, Hofstetter WL, Ajani JA, Cox JD. Intensity-modulated proton therapy further reduces normal tissue exposure during definitive therapy for locally advanced distal esophageal tumors: a dosimetric study. Int J Radiat Oncol Biol Phys. 2011 Dec 1;81(5):1336-42. doi: 10.1016/j.ijrobp.2010.07.2001. Epub 2011 Apr 4. PMID: 21470796

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9. Wei X, Liu HH, Tucker SL, Wang S, Mohan R, Cox JD, Komaki R, Liao Z. Risk factors for pericardial effusion in inoperable esophageal cancer patients treated with definitive chemoradiation therapy. Int J Radiat Oncol Biol Phys. 2008 Mar 1;70(3):707-14. doi: 10.1016/j.ijrobp.2007.10.056. Epub 2008 Jan 11. PMID:18191334

10. Wang SL, Liao Z, Vaporciyan AA, Tucker SL, Liu H, Wei X, Swisher S, Ajani JA, Cox JD, Komaki R. Investigation of clinical and dosimetric factors associated with postoperative pulmonary complications in esophageal cancer patients treated with concurrent chemoradiotherapy followed by surgery. Int J Radiat Oncol Biol Phys. 2006 Mar 1;64(3):692-9. Epub 2005 Oct 19. PMID: 16242257

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Gastrointestinal (GI) Cancer
Recommended Proton Therapy Indications

Indications:

1) **Hepatocellular Carcinoma**

2) **Intrahepatic Cholangiocarcinoma**

Inclusion criteria:

- Clinical stage T1-4 N0-1 M0

- Curative treatment intent

- Definitive radiotherapy receiving doses ≥ 40 Gy

- ECOG performance status 0-2

- Child-Pugh score A or B

- Dose-volume parameters for photon RT are unable to meet mean liver (defined as liver – gross tumor volume) dose constraints specified on RTOG 1112 (Hepatocellular Carcinoma) and NRG GI001 (Cholangiocarcinoma)

    - 5 fractions: mean liver dose ≤ 13 Gy; V10<70%;

    - 15 fractions: mean liver dose ≤ 22 Gy

Exclusion criteria:

- Clinical stage Tx, Nx, M1

- Treatment intent is palliative

- Total radiotherapy dose is < 40 Gy

Scientific evidence:

1. Bush DA, Hillebrand DJ, Slater JM, Slater JD. High-dose proton beam radiotherapy of hepatocellular carcinoma: preliminary results of a phase II trial. Gastroenterology. 2004 Nov;127(5 Suppl 1):S189-93. PMID: 15508084
2. Bush DA, Kayali Z, Grove R, Slater JD. The safety and efficacy of high-dose proton beam radiotherapy for hepatocellular carcinoma: a phase 2 prospective trial. Cancer. 2011 Jul 1;117(13):3053-9. doi: 10.1002/cncr.25809. Epub 2011 Jan 24. PMID: 21264826

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4. Dionisi F, Ben-Josef E. The use of proton therapy in the treatment of gastrointestinal cancers: liver. Cancer J. 2014 Nov-Dec;20(6):371-7. doi: 10.1097/PPO.0000000000000082. PMID: 25415681[PubMed - in process]

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10. Hata M, Tokuuye K, Sugahara S, Kagei K, Igaki H, Hashimoto T, Ohara K, Matsuzaki Y, Tanaka N, Akine Y. Proton beam therapy for hepatocellular carcinoma with portal vein tumor thrombus. Cancer. 2005 Aug 15;104(4):794-801. PMID: 15981284

11. Hong TS, DeLaney TF, Mamon HJ, Willett CG, Yeap BY, Niemierko A, Wolfgang JA, Lu HM, Adams J, Weyman EA, Arellano RS, Blaszkowsky LS, Allen JN, Tanabe KK, Ryan DP, Zhu AX. A prospective feasibility study of respiratory-gated proton beam therapy for liver tumors. Pract Radiat Oncol. 2014 Sep-Oct;4(5):316-22. doi: 10.1016/j.prro.2013.10.002. Epub 2013 Nov 22. PMID: 25194100

12. Kim TH, Park JW, Kim YJ, Kim BH, Woo SM, Moon SH, Kim SS, Koh YH, Lee WJ, Park SJ, Kim JY, Kim DY, Kim CM. Phase I dose-escalation study of proton beam therapy for inoperable hepatocellular carcinoma. Cancer Res Treat. 2015 Jan;47(1):34-45. doi: 10.4143/crt.2013.218. Epub 2014 Sep 11. PMID: 25381830 [PubMed]

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23. Sugahara S, Oshiro Y, Nakayama H, Fukuda K, Mizumoto M, Abei M, Shoda J, Matsuzaki Y, Thono E, Tokita M, Tsuboi K, Tokuuye K. Proton beam therapy for large hepatocellular carcinoma. Int J Radiat Oncol Biol Phys. 2010 Feb 1;76(2):460-6. doi: 10.1016/j.ijrobp.2009.02.030. Epub 2009 May 7. PMID: 19427743

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27. Hong, MGH, ongoing prospective trial.

Hematologic Cancer
Recommended Proton Therapy Indications

Indications:
1) **Hodgkin Lymphoma** or **Non-Hodgkin Lymphoma that involves the mediastinum**
2) **Hodgkin Lymphoma or Non-Hodgkin Lymphoma in non-mediastinal sites where proton therapy would likely reduce the risk of pneumonitis or late effects such as secondary malignancy or cardiovascular disease, or other chronic health conditions compared with conventional radiation therapy.**

- In patients with lymphoma, in most clinical settings, there is a definite, but modest benefit for treatment with radiation therapy. Because the benefit is often modest, it is critical that treatment-related toxicity be minimal. The most frequent causes of death in patients who survive HL 10 years are treatment related with significant excesses of both second malignancy and cardiovascular disease. [1,2] Proton therapy is indicated if it will decreases the risk of treatment-related radiation pneumonitis, or late effects such as heart disease or second malignancy.

- Studies of radiation-related heart disease strongly suggest that increasing dose to the heart increases the risk of cardiac complications. [3-7] These studies strongly suggest that there is no threshold below which there is no risk, with mean heart doses as low as 1 to 4 Gy resulting in significant increases in cardiac morbidity and mortality. [3-7]

- Studies of second malignancy suggest that doses as low as 1 to 4 Gy to normal tissues are associated with an increase the risk of second malignancy (Travis, Travis, Neglia, van den Belt-Desebout) and that there is a linear relationship with no dose threshold. [8-11]

- Radiation pneumonitis and late pulmonary toxicities are correlated with mean lung dose, with an increased risk of pneumonitis for mean lung doses ≥ 12 Gy or V13 ≥22%. [12]

- Multiples comparative studies of proton and photon therapy have shown benefits protons in the likely reduction of risks for secondary cancer and cardiovascular disease (Chera, Hoppe X3, Jorgenson, Li, Maraldo, Schneider. Summaries of the benefits of proton therapy are provided below with each publication reference in the Scientific Evidence section. [13-20]

Inclusion criteria:
- Patients with mediastinal or non-mediastinal lymphoma will be eligible for treatment with protons if:
  - protons lower the mean lung dose from ≥ 12 Gy with optimized 3D or IMRT to ≤12 Gy with protons

- o protons lower the volume of lung receiving 13 Gy from ≥ 22% with optimized 3D or IMRT to ≤22% with protons

- o protons result in a ≥ 1 Gy reduction in the average dose to the heart

- o protons lower the mean dose to breast, stomach, brain, or other organ by ≥ 1 Gy .

Exclusion criteria:
- Lymphoma that is beyond any reasonable hope of cure *unless* :

  - o protons lower the mean lung dose from ≥ 12 Gy with optimized 3D or IMRT to ≤12 Gy with protons

  - o protons lower the volume of lung receiving 13 Gy from ≥ 22% with optimized 3D or IMRT to ≤22% with protons

Scientific Evidence:

1. Oeffinger KC, Mertens AC, Sklar CA, Kawashima T, Hudson MM, Meadows AT, Friedman DL, Marina N, Hobbie W, Kadan-Lottick NS, Schwartz CL, Leisenring W, Robison LL. Chronic health conditions in adult survivors of childhood cancer. N Engl J Med 2006. 355(15): 1572-82.

   - Among survivors, the cumulative incidence of a chronic health condition reached 73.4% 30 years after the cancer diagnosis.

2. Castellino SM, Geiger AM, Mertens AC, Leisenring WM, Tooze JA, Goodman P, Stovall M, Robison LL, Hudson MM. Morbidity and mortality in long-term survivors of Hodgkin lymphoma: a report from the Childhood Cancer Survivor Study. Blood 2011. 117: (6): 1806-16.

   - There is an excess of overall mortality, death from second malignant neoplasms and cardiovascular disease in survivors of Hodgkin lymlphoma with persists >20 years after treatment.

3. Char ZA, et al. Coronary heart disease after radiotherapy for peptic ulcer disease. Int J R Oncol Biol Phys 61:842-850, 2005

   - *A statistically significant relationship was observed between coronary heart disease average dose to the heart in the 0-7.6 Gy range. The study is important in that it shows that even very low doses (2 Gy or more) may be associated with increased risk of coronary artery heart disease.*

4. Darby, SC, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. New Eng J Med 11:987-998, 2013

   - *Cardiac risk strongly related to cardiac dose with no obvious threshold*

5. Hancock, et al. Factors affecting later mortality from heart disease after treatment of Hodgkin's Disease. JAMA. 270:1949-1955, 1993:.

   - *A cardiac dose of more than 30 Gy was associated with a three-fold higher risk of death from cardiac disease.*

6. Mulrooney DA, Yeazel MW, Kawashima T, Mertens AC, Mitby P, Stovall M, Donaldson SS, Green DM, Sklar CA, Robison LL, Leisenring WM. Cardiac outcomes in a cohort of adult survivors of childhood and adolescent cancer: retrospective analysis of the Childhood Cancer Survivor Study cohort. BMJ 2009. 339.

   - Cardiac radiation exposure of 15 Gy or more increased the relative hazard of congestive heart failure, myocardial infarction, pericardial disease, and valvular abnormalities by twofold to sixfold compared to non-irradiatied survivors.

7. Tukenova M, Guibout C, Oberlin O, Doyoon F, Mousannif A, Haddy N, Guierin S, Pacquement H, Aouba A, Hawkins M, Winter D, Bourhis J, Lefkopoulos D, Diallo I, De Vathaire F. Role of cancer treatment in long-term overall and cardiovascular mortality after childhood cancer. J Clin Oncol. 2010.. 28(8): 1308-15.

   - *A cardiac dose of more than 5 Gy was associated an increase relative risk of cardiac mortality of 12.5 and of 25 for >15 Gy to the heart.*

8. Travis LB, Hill DA, Dores GM, Gospodarowicz M, van Leeuwen FE, Holowaty E, Glimelius B, Andersson M, Wiklund T, Lynch CF, Van't Veer MB, Glimelius I, Storm H, Pukkala E, Stovall M, Curtis R, Boice JD, Jr, Gilber E. Breast cancer following radiotherapy and chemotherapy among young women with Hodgkin disease. JAMA 2003. 290(4): 465-475.
   - *A radiation dose of 4 Gy or more to the breast was associated with a 3.2 fold increased risk of breast cancer in HD survivors. The dose response was linear.*

9. Travis LB, Gospodarowicz M, Curtis RE. et al. Lung cancer following chemotherapy and radiotherapy for Hodgkin's disease. *J Natl Cancer Inst.*2002;94:182-192.
   - *A radiation dose of 5 Gy or more was associated with a 5.9 fold increased relative risk of lung cancer in Hodgkin's disease survivors; the dose response was linear.*

10. Neglia JP, Robison LL, Stovall M, Liu Y, Packer RJ, Hammond S, Yasui Y, Kasper CE, Mertens AC, Donaldson SS, Meadows AT, Inskip PD. New primary neoplasms of the central nervous system in survivors of childhood cancer: a report from the Chidhod Cancer Survivor Study. J natl Cancer Inst 2006 98(21): 1528-37.

    - *Radiation exposure was associated with increased rsk of subsequent glioma (OR = 6.78) and meningioma (OR = 9.94) with a linear relative risk dose response.*

11. Van den Belt-Desebout, Aleman BM, Besseling G, de Bruin ML, Haupfmann M, van't Veer MB, de Wit R, Ribot JG, Noordijk EM, Kerst JM, Gietema JA, van Leeuwen FE. Roles of radiation dose and chemotherapy in the etiology of stomach cancer as a second malignancy. Int J Radiat Oncol Biol Phys 2009. 75(5): 1420-9.

    - *The risk of stomach cancer after treatment for Hodgkin's lymphoma or testicular cancer increased with increasing mean stomach dose at an estimated relative risk of 0,84 per Gy.*

12. Sepenwoolde Y, et al. Comparing different NTCP models that predict the incidence of radiation pneumonitis. Int J Rad Oncol Biol Phys 55:724-735, 2003.

- *The risk of radiation pneumonitis in 382 patients with breast cancer, lymphoma and lung cancer was assessed in relation to a variety of measures of radiation dose to the lungs. The risk of pneumonitis was estimated to be more than 5% if the mean lung dose was greater than approximately 12 Gy or if the volume of lung receiving more than 13 Gy (V13) was more than 23% (see Figure 2).*

13. Chera, et al. Dosmetric comparison of three different involved nodal irradiation techniques for stage II Hodgkin's lymphoma patients: Conventional radiotherapy, intensity-modulated radiotherapy and three-dimensional proton radiotherapy. Int. J. Radiation Oncology Biol. Phys., Vol. 75, No. 4, pp. 1173–1180, 2009

- *Mean breast dose lower; 1.94 Gy for CRT, 3.74 Gy for IMRT, 1.59 Gy for 3DPRT.*

- *Mean lung dose: 4.83, 5.38 and 30.4*

- *In general, the advantage for protons is seen in volume receiving relatively low dose (<15 Gy, see figures 3, 4 and 5).*

14. Hoppe, Bradford et al, Involved-Node Proton Therapy in Combined Modality Therapy for Hodgkin Lymphoma: Results of a Phase 2 Study. Int J Radiation Oncol Biol Phys, Vol. 89, No. 5, pp. 1053e1059, 2014

- *Progressively lower average integral dose, and average dose to heart, lungs, breast, thyroid and esophagus when 3D, IMRT and proton plans were compared in 15 patients treated with INPT after chemotherapy. Three year EFS 93%.*

15. Hoppe, Bradford, et al. Effective dose reduction to cardiac structures using protons compared with 3DCRT and IMRT in mediastinal Hodgkin Lymphoma. Int J Radiation Oncol Biol Phys, Vol. 84, No. 2, pp. 449e455, 2012

- *Highly significant decrease in dose with comparison of PT vs 3D or IMRT to multiple critical organs with proton therapy, including heart, L ventricle, R ventricle, L atrium, mitral valve, tricuspid valve, aortic valve (significant only for 3D vs PT), LAD, L circumflex, R circumflex (significant only for 3D vs PT), pulmonary artery (significant only for 3D vs PT), and ascending aorta (significant only for IMRT vs PT).*

16. Hoppe, Bradford, et al. Consolidative Involved-Node Proton Therapy for Stage IA-IIIB Mediastinal Hodgkin Lymphoma Preliminary Dosimetric Outcomes From a Phase II Study. Int J Radiation Oncol Biol Phys, Vol. 83, No. 1, pp. 260e267, 2012

- *"PT provided the lowest mean dose to the heart, lungs, and breasts for all 10 patients compared with either 3D-CRT or IMRT."*

17. Jorgensen, et al. The effect of esophagus after different radiotherapy techniques for early stage Hodgkin's lymphoma. Acta Oncologica, 52: 1559–1565, 2013

- *"Mean dose to the esophagus was 16.4, 16.4, 14.7 and 34.2 Gy (p 0.001) with 3DCRT, VMAT, PT and MF treatment, respectively. No differences were seen in the estimated risk of developing esophagitis, stricture or cancer with 3DCRT compared to VMAT (p =1.000, p =1.000, p = 0.356). PT performed significantly better with the lowest risk estimates on all parameters compared to the photon treatments, except compared to 3DCRT for stricture (p = 0.066)."*

18. Li, et al. [Rationale for and preliminary results of proton beam therapy for mediastinal lymphoma](). International Journal of Radiation Oncology, Biology, Physics. 81(1):167-74, 2011

    - *10 patients, "PBT delivered lower mean doses to the lung (6.2 vs. 9.5 Gy), esophagus (9.5 vs. 22.3 Gy), and heart (8.8 vs. 17.7 Gy) but not the breasts (5.9 vs. 6.1 Gy) than did conventional RT."*

19. Maraldo, et al. [Estimated risk of cardiovascular disease and secondary cancers with modern highly conformal radiotherapy for earl-stage mediastinal Hodgkin lymphoma](). Annals of Oncology 24: 2113–2118, 2013

    - *Compared to arc IMRT (VMAT) or 3D conventional therapy, highly significant estimated benefit for protons as measured by cardiac mortality, cardiac morbidity, MI, valvular disease (only VMAT vs PT significant), lung ca, breast ca and life years lost.*

20. Scheneider, et al. [Comparative risk assessment of secondary cancer incidence after treatment of Hodgkin's disease with photon and proton radiation](). Radiation Research 154, 382--388 (2000)

    - *This is basically a case report in which the risk of second cancer is calculated for several different kinds of plans (2 field photons, IMRT, and two different proton plans). "Irradiation with protons using the spot scanning technique decreases the avoidable cancer incidence compared to photon treatment by a factor of about two."*

<div align="center">

Prostate Cancer
Recommended Proton Therapy Indications

</div>

Indications:

1) Delivering a high radiation dose to the primary tumor in the prostate and/or seminal vesicles has become an important aspect of the optimal management of clinically localized prostate carcinoma in the radiotherapy setting. This is the result of multiple phase III studies demonstrating that a higher radiation dose reduces the risk of prostate cancer recurrence[1-6]. However, a higher radiation dose is inherently associated with an increased risk of radiation-related gastrointestinal and genitourinary toxicity[1-6]. Unlike conventional X-rays, protons have a physical property to deposit most of their energy only when they reach their target. This allows protons to deliver a radiation dose to the target more preferentially, while minimizing a dose to the nearby normal organs. Thus, a delicate balance of delivering a high radiation dose to eradicate prostate cancer while largely sparing the nearby normal organs (such as rectum and bladder) can be achieved much better with proton therapy than with conventional x-rays.

2) Proton therapy can be at least as efficacious as conventional external beam radiotherapy in treating clinically localized (encompassing low-risk, intermediate-risk, and high-risk) prostate cancer, while reducing the risk of acute and late side effects of radiotherapy[6-8, 14]. At present, a phase III study is in progress to compare proton therapy with conventional external beam radiotherapy using intensity modulated radiotherapy (IMRT). Table 1 depicts the comparison between conventional external beam radiotherapy and proton therapy with respect to therapeutic efficacy in terms of biochemical relapse-free rate, based on some of published manuscripts and abstracts. Biochemical relapse [also called 'PSA (prostate specific antigen) relapse'] is a widely accepted surrogate representing prostate cancer recurrence. Table 2 compares the incidences of acute and late radiation toxicity between conventional external beam radiotherapy and proton therapy. Additionally, the comparison of patient-reported quality of life between two prospectively collected databases suggests approximately 50% reduction in problems with significant bowel urgency and frequency in patients treated with proton therapy compared with IMRT[13].

3) Clinical and laboratory studies have suggested that prostate cancer has a relatively slow rate of proliferation, characterized by a low α/β value (1.5 to 3 Gy) in a linear quadratic model for cell survival after irradiation. This implies that a larger radiation dose per fraction (i.e. hypofractionation) is more effective in cell killing for prostate cancer than simply adding more fractions. Another major advantage of hypofractionation is its convenience and cost effectiveness, as it allows a shorter treatment duration with a reduced number of radiation fractions. Table 3 shows phase III studies comparing a conventional dose-fractionation regimen with a moderate hypofractionation regiment in a conventional external beam setting. It has been shown that a moderate hypofractionation regimen can be efficacious as a conventional dose-fractionation schedule without an increase in the risk of radiation morbidity. Thus, in a proton therapy setting, the incorporation of a moderate hypofractionation regimen is appropriate for properly selected clinical situations. The University of Florida recently submitted an abstract to the annual meeting of 2015 ASTRO that describes the outcome of a prospective trial of hypofractionated proton therapy in 228 men with low- or intermediate-risk prostate cancer who had 5 years of follow-up. This study reports that a hypofractionated proton therapy (28-29 fractions over 5 ½ weeks) can yield outcomes

similar to those achieved with a standard fractionation proton therapy (39-42 fractions over 8 weeks) in selected patients [15]. Patient included in the trial were men with prostates < 60 cc in volume, IPSS (International Prostate Sympton Score) <15, and no previous required treatment with either alpha reductase inhibitors (Flomax, Hytrin, etc) or anticoagulation (Plavix, Coumadin, etc). This hypofractionation strategy would be similar in cost to standard fractionation IMRT, but more convenient for patients and potentially yielding better disease control and quality of life.

Inclusion criteria:

- Age ≥ 18 years

- Histologic confirmation of prostate cancer

- Low, intermediate, or high risk prostate cancer without evidence of distant metastases

- When regional pelvic node irradiation is required in patients with high risk disease, proton therapy can be used for both the pelvic nodes and the prostate, or as a prostate boost following conventional external beam radiotherapy to the pelvic nodes.

- Whenever clinically appropriate, a moderate hypofractionation regimen (26 to 28 fractions) can be utilized to maximize cost-effectiveness of proton therapy.

- Clinically palpable or radiographically evident local recurrence of prostate cancer following radical prostatectomy for which definitive salvage radiotherapy is indicated

- Special circumstances in which definitive radiation is required, and the effort to minimize a radiation dose to normal organs is critically important due to other co-morbid medical issues: patients with inflammatory bowel disease, prior pelvic irradiation for non-prostate cancer, or hip prosthesis.

Exclusion criteria:

- Presence of distant metastasis

- Medical contraindication to receipt of radiotherapy.

- Severe active co-morbid systemic illnesses or other severe concurrent disease which, in the judgment of the clinician, would make the patient inappropriate for radiotherapy.

- Very low risk prostate cancer (CST1C and PSA <10 and PSA index <0.15 and <3 cores involved and <50% maximum core involvement and Gleason ≤6) and life expectancy of < 10 years.

Scientific Evidence:

1. Al-Mamgani A, van Putten WL, Heemsbergen WD, van Leenders GJ, Slot A, Dielwart MF, et al. Update of Dutch multicenter dose-escalation trial of radiotherapy for localized prostate cancer. Int J Radiat Oncol Biol Phys. 2008;72:980-8.

2. Beckendorf V, Guerif S, Le Prise E, Cosset JM, Bougnoux A, Chauvet B, et al. 70 Gy versus 80 Gy in localized prostate cancer: 5-year results of GETUG 06 randomized trial. Int J Radiat Oncol Biol Phys. 2011;80:1056-63.

3. Dearnaley DP, Sydes MR, Graham JD, Aird EG, Bottomley D, Cowan RA, et al. Escalated-dose versus standard-dose conformal radiotherapy in prostate cancer: first results from the MRC RT01 randomised controlled trial. Lancet Oncol. 2007;8:475-87.

4. Kuban DA, Tucker SL, Dong L, Starkschall G, Huang EH, Cheung MR, et al. Long-term results of the M. D. Anderson randomized dose-escalation trial for prostate cancer. Int J Radiat Oncol Biol Phys. 2008;70:67-74.

5. Michalski J, Moughan J, Purdy J, Bosch W, Bahary J-P, Lau HY, et al. A randomized trial of 79.2Gy versus 70.2Gy radiation therapy (RT) for localized prostate cancer [abstract]. J Clin Oncol 33, 2015 (suppl 7, abstr 4).

6. Zietman AL, Bae K, Slater JD, Shipley WU, Efstathiou JA, Coen JJ, et al. Randomized trial comparing conventional-dose with high-dose conformal radiation therapy in early-stage adenocarcinoma of the prostate: long-term results from proton radiation oncology group/american college of radiology 95-09. J Clin Oncol. 2010;28:1106-11.

7. Mendenhall NP, Hoppe BS, Nichols RC, Mendenhall WM, Morris CG, Li Z, et al. Five-year outcomes from 3 prospective trials of image-guided proton therapy for prostate cancer. Int J Radiat Oncol Biol Phys. 2014;88:596-602.

8. Slater JD, Rossi CJ, Jr., Yonemoto LT, Bush DA, Jabola BR, Levy RP, et al. Proton therapy for prostate cancer: the initial Loma Linda University experience. Int J Radiat Oncol Biol Phys. 2004;59:348-52.

9. Pollack A, Walker G, Horwitz EM, Price R, Feigenberg S, Konski AA, et al. Randomized trial of hypofractionated external-beam radiotherapy for prostate cancer. J Clin Oncol. 2013;31:3860-8.

10. Arcangeli S, Strigari L, Gomellini S, Saracino B, Petrongari MG, Pinnaro P, et al. Updated results and patterns of failure in a randomized hypofractionation trial for high-risk prostate cancer. Int J Radiat Oncol Biol Phys. 2012;84:1172-8.

11. Michalski JM, Yan Y, Watkins-Bruner D, Bosch WR, Winter K, Galvin JM, et al. Preliminary toxicity analysis of 3-dimensional conformal radiation therapy versus intensity modulated radiation therapy on the high-dose arm of the Radiation Therapy Oncology Group 0126 prostate cancer trial. Int J Radiat Oncol Biol Phys. 2013;87:932-8.

12. Arcangeli G, Fowler J, Gomellini S, Arcangeli S, Saracino B, Petrongari MG, et al. Acute and Late Toxicity in a Randomized Trial of Conventional Versus Hypofractionated Three-Dimensional Conformal Radiotherapy for Prostate Cancer. Int J Radiat Oncol. 2011;79:1013-21.

13. Hoppe BS, Michalski JM, Mendenhall NP, Morris CG, Henderson RH, Nichols RC, et al. Comparative effectiveness study of patient-reported outcomes after proton therapy or intensity-modulated radiotherapy for prostate cancer. Cancer. 2014;120:1076-82.

14. Nihei K, Ogino T, Onozawa M, Murayama S, Fuji H, Murakami M, et al. Multi-institutional phase II study of proton beam therapy for organ-confined prostate cancer focusing on the incidence of late rectal toxicities. Int J Radiat Oncol Biol Phys. 2011;81:390-6

15. Henderson RH, personal communication from abstract submitted to ASTRO for 2015 fall meeting.

Appendix:

Table 1: Comparison between photon vs. proton for biochemical relapse-free rate, based on some of the prospective studies

Study	F/U (years)	N	Treatment	Biochemical relapse-free rate
Photon				
RTOG0126 (2015)[5]	7	748	79.2 Gy in 44 fractions (intermediate risk)	84% at 5 years
Fox Chase Cancer Center (2013)[9]	5.7	153	76 Gy in 38 fractions (mainly, intermediate- and high-risk)	78.6% at 5 years
Italy (2012)[10]	5.8	85	80 Gy in 40 fractions (intermediate- and high-risk)	79% at 5 years

Study	F/U (years)	N	Treatment	Biochemical relapse-free rate
Proton				
Univ. Florida (2014)[7]	5.2	211	78 GyE (Gy): low risk 78-82 GyE (Gy): intermediate risk 78 GyE (Gy) + weekly docetaxel + 6-month ADT: high risk	99% at 5 yrs for low risk; 99% at 5 yrs for intermediate risk; 76% at 5 yrs for high risk
Japan (2011)[14]	3.6	151	74GyE in 37 fractions (low- and intermediate-risk)	94% at 3 years
Proton Radiation Oncology Group (2010)[6]	8.9	197	28.8 GyE in 16 fractions (proton) + 50.4 Gy in 28 fractions (photon) (low- and intermediate-risk)	82.6% at 10 years

ADT: Androgen deprivation therapy

Table 2: Comparison between photon vs. proton for radiation toxicity

Study	Tool for toxicity assessment	RT dose	F/U (yrs)	N	Acute toxicity				Late toxicity			
					GI		GU		GI		GU	
					G2	≥ G3	G2	≥ G3	G2	≥ G3	G2	≥ G3
Photon												
RTOG0126 (IMRT) (2013)[11]	CTCAE v2.0 and RTOG/EORTC	79.2 Gy in 44 f	3.5	257	≥ G2 GI or GU: 9.7%				≥ G2: 15.1% at 3 yrs	≥ G3: 2.6% at 3 yrs		
RTOG0126 (IMRT/3D-CRT) (2015)[5]			7	748	≥ G2 GI: 2.4%		≥ G2 GU: 11.1%		≥ G2: 21% at 5 yrs	≥ G3: 5% at 5 yrs	≥ G2: 12% at 5 yrs	≥ G3: 3% at 5 yrs
Fox Chase Cancer Center (IMRT) (2013)[9]	LENT/RTOG (similar to CTCAE v4.0)	76 Gy in 38 f	5.7	153					20.5% at 5 yrs	2% at 5 yrs	≥ G2: 37.9% at 5 yrs (or 13.4% with modified criteria)	
		70.2 Gy in 26 f		154					16.1% at 5 yrs	2% at 5 yrs	≥ G2: 39.1% at 5 yrs (or 21.5% with modified criteria)	
Italy (3D-CRT) (2011)[12]	RTOG/EORTC for acute toxicity; LENT-SOMA for late toxicity	80 Gy in 40 f	2.9	85	≥ G2 GI: 21%		≥ G2 GU: 40%		≥ G2 rectal: 12%		≥ G2 GU: 6%	
		62 Gy in 20 f	2.7	83	≥ G2 GI: 35%		≥ G2 GU: 47%		≥ G2 rectal: 14%		≥ G2 GU: 8%	
Proton												
Univ. Florida (2014)[7]	CTCAE v3.0	78-82 GyE	5.2	211		0.5%		0.5%		1% at 5 yrs (0.5%, if CTCAE v4.0)		5.4% at 5 yrs (0.9%, if CTCAE v4.0)
Japan (2011)[14]	CTCAE v2.0	74 GyE	3.6	151	0.7%	0%	12%	0%	2% at 2 yrs	0% at 2 yrs	4.1% at 2 yrs	0% at 2 yrs

Table 3: Phase III studies evaluating hypofractionation regimens: photons

Study	F/U (years)	Patients	N	Treatment	Biochemical relapse-free rate	
Fox Chase Cancer Center (2013)[9]	5.7	Low- to High-risk; (mainly, intermediate- and high-risk); (ADT for intermediate- and high-risk)	153	76 Gy in 38 fractions (2 Gy/f)	78.6% at 5 years	P = 0.745
			154	70.2 Gy in 26 fractions (2.7 Gy/f)	76.7% at 5 years	
Italy (2012)[10]	5.8	Intermediate- and High-risk; (all had 9-month ADT)	85	80 Gy in 40 fractions (2 Gy/f)	79% at 5 years	P = 0.065
			83	62 Gy in 20 fractions over 5 weeks (4 fractions/week) (3.1 Gy/f)	85% at 5 years	

ADT: Androgen deprivation therapy

Thoracic Cancer
Recommended Proton Therapy Indications

Indications:

1) **Stage III Lung cancer,** which is pathologically confirmed.

Inclusion criteria:

- Specific dosimetric conditions must be present for a patient to be qualified to receive PBT rather than Conventional radiotherapy (C-RT (either Intensity modulated RT or 3D-RT)). This will require generating comparative plans demonstrating any one of the following:
  - PBT keeps the mean lung dose < 20 Gy when conventional radiotherapy cannot. (C-RT=3D-RT or IMRT)
    - This will keep the risk of grade $\geq$3 radiation pneumonitis to <20% instead of >30%; Wang et al.[1])
  - PBT keeps the V20 (Volume of lung receiving $\geq$20 Gy) less than 30% when C-RT cannot.
    - This will keep pneumonitis fatalities to $\leq$1% instead of $\geq$2.9% (Palma et al.[2])
  - PBT is indicated to spare cardiac toxicity/fatalities by reducing V5 (volume of heart receiving $\geq$5Gy) &/or V30
    - RTOG 0617 found these were associated with survival[3]. However, the exact cut-offs have not been firmly established. This will likely be defined in the next 2 years.
  - PBT is indicated to spare cardiac toxicity by reducing the mean cardiac dose to <13.5 Gy when C-RT cannot.
    - This will keep long term cardiac event to less than 2x the normal risk (ref. Darby[4])
  - PBT can keep the V60 for the esophagus to <17% when C-RT cannot.
    - This will keep the incidence of grade $\geq$ 3 radiation esophagitis to $\leq$10% instead of 22% (Palma et al.[5]).

Exclusion criteria:

- Patients treated for palliation alone (generally this is with doses less than 60 Gy and often without chemotherapy)

- Stage I lung cancer
  - Indications:
    - Stage I (T2N0M0) lung cancer, when treated in a hypofractionated fashion
    - Stage I (T1N0M0) lung cancer, treated in a hypofractionated fashion, if organ-at-risk constraints cannot be met with photon SBRT

Inclusion criteria:

Protons are appropriate for patients with T2N0 non-small cell lung cancer, when given in a hypofractionated course. Protons given in SBRT/SABR or hypofractionated course may be appropriate for T1N0, if the following parameters cannot be met with IMRT/ 3-D conformal techniques:

- Lung V5 – 40%
- Lung V20 – 20%
- Heart maximum dose 40 Gy
- Spinal cord maximum dose 20 Gy
- Bronchial tree maximum dose 40 Gy

Scientific Evidence:

In an analysis of compiled data from a national database, patients with T2N0 non-small cell lung cancer treated with higher effective doses of SBRT (stereotactic body radiation therapy) – significantly better overall survival at 2 and 4 years.[6] Survivals at 2 years were approximately 57% for higher biologically equivalent doses vs 40% for lower doses, and at 4 years the differences persisted (approximately 35% vs 20%). In a review from multiple series of patients who have received high dose (high BED) protons as stereotactic ablative treatment (SABR) or hypofractionated treatment (typically 10 or fewer treatments), the two year overall survivals are 95-98%, 3 year survivals are 60-90%, with 4 years survival of 51%.[7] In addition, planning studies show that many of the patients with centrally located T1 or T2 lesions are not candidates for SBRT/SABR with x-rays, because of the inability to meet dose constraints for heart, esophagus, lungs, brachial plexus or bronchial tree.[8]

1. Wang S, Liao Z, Wei X, et al. Analysis of clinical and dosimetric factors associated with treatment-related pneumonitis (TRP) in patients with non-small-cell lung cancer (NSCLC) treated with concurrent chemotherapy and three-dimensional conformal radiotherapy (3D-CRT). Int J Radiat Oncol Biol Phys. 2006;66: 1399-1407.

2. Palma DA, Senan S, Tsujino K, et al. Predicting radiation pneumonitis after chemoradiation therapy for lung cancer: an international individual patient data meta-analysis. Int J Radiat Oncol Biol Phys. 2013;85: 444-450.

3. Bradley JD, Paulus R, Komaki R, et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. Lancet Oncol. 2015;16: 187-199.a

4. Darby SC, Ewertz M, McGale P, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. N Engl J Med. 2013;368: 987-998.

5. Palma DA, Senan S, Oberije C, et al. Predicting esophagitis after chemoradiation therapy for non-small cell lung cancer: an individual patient data meta-analysis. Int J Radiat Oncol Biol Phys. 2013;87: 690-696.

6. Koshy et al, Increasing radiation therapy dose is associated with improved survival in patients undergoing stereotactic body radiation therapy for stage I non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2015; 91:344-50.

7. Grant JD, Chang JY. Proton-based stereotactic ablative radiotherapy in early-stage non-small-cell lung cancer. Biomed Res Int, 2014; 2014:389048, doi:10.1155/2014/389048, Epub 2014 Jul 17.

8. Register, et al, Proton stereotactic body radiation therapy for clinically challenging cases of centrally and superiorly located stage I non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2010; 80:1015-22.