Exercise Rehabilitation Following a Cancer Diagnosis: Cardiorespiratory Fitness to Prognosis Outcomes

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Introduction

- Therapeutic properties of exercise been recognized since ancient Greeks and Chinese
- 1995 American College of Sports Medicine (ASCM) – first exercise px guidelines for US adults
- Exercise is the cornerstone of numerous disease pathologies; many conditions are qualifying dx for exercise rehabilitation
- Comparably less attention in the role of exercise following a cancer diagnosis, until recently….

Jones, AICR, 2011

Rapid emergence of cancer survivorship

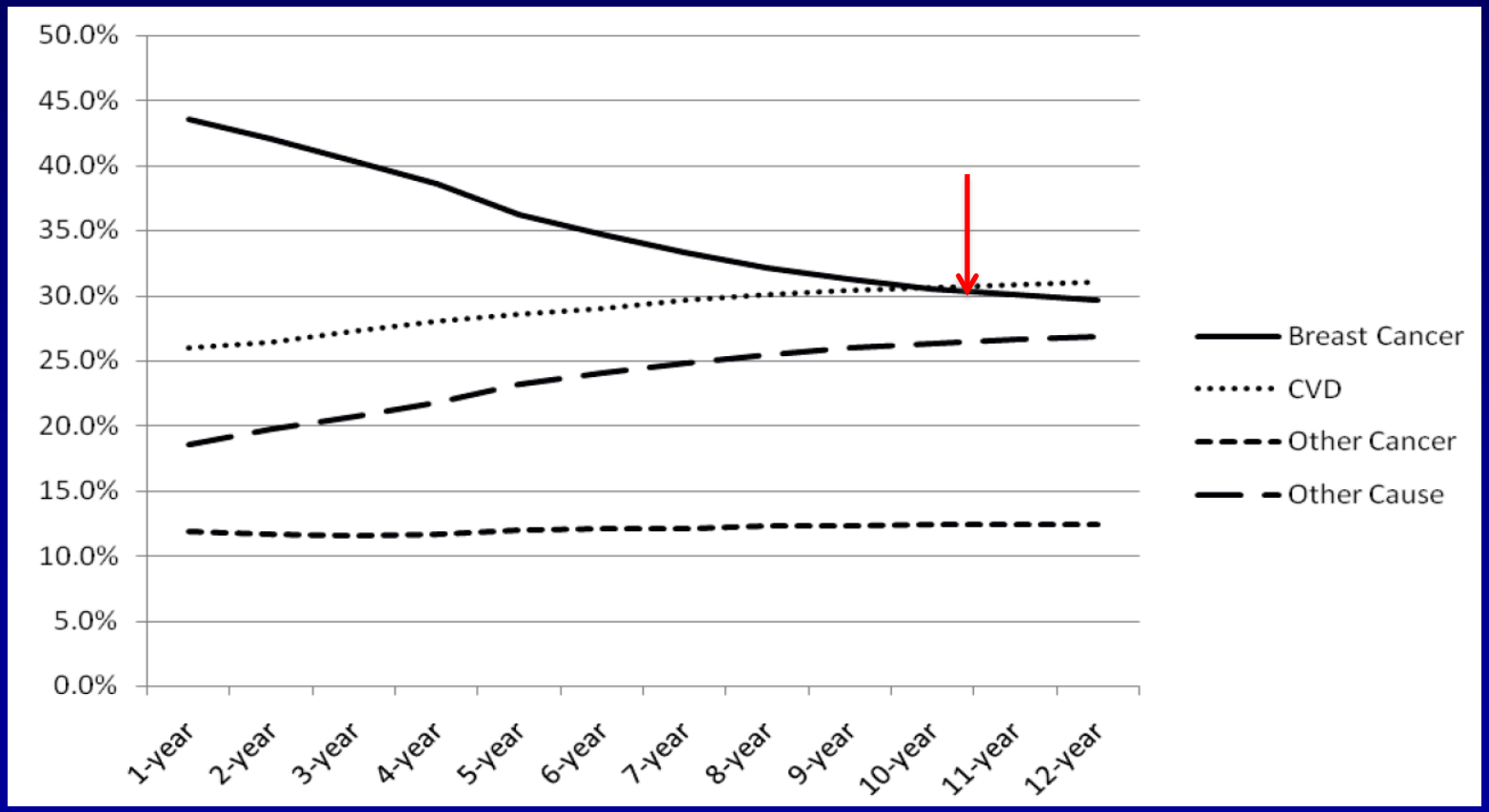
Site	1975 (%)	2009 (%)	% increase
Overall	50	67	17
Childhood	30	79	49
Prostate	67	99	32
Breast	75	91	16
Colon	49	66	17
Lung	12	16	4

- ~13m cancer survivors in the US (~25m worldwide)
- Projected to explode with further improvements & aging population
- Increased risk of the late-effects of cancer therapy

Jones, AICR, 2011

CVD – impt competing cause of mortality

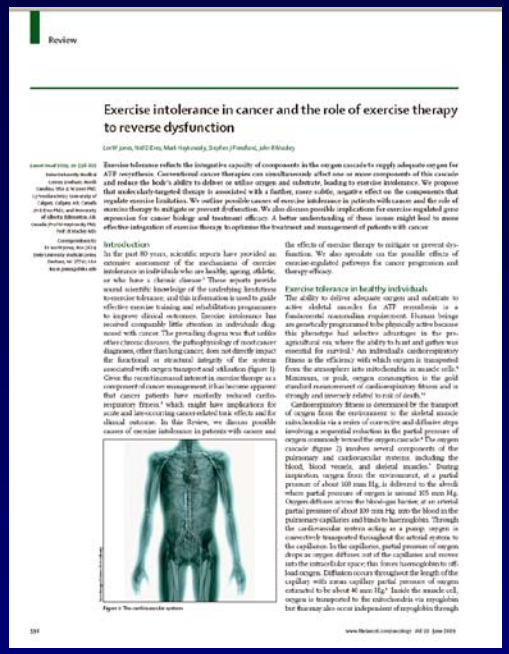
- Early-stage breast cancer pts x2 as likely to die from competing causes compared with breast cancer
  - CVD – leading cause of death



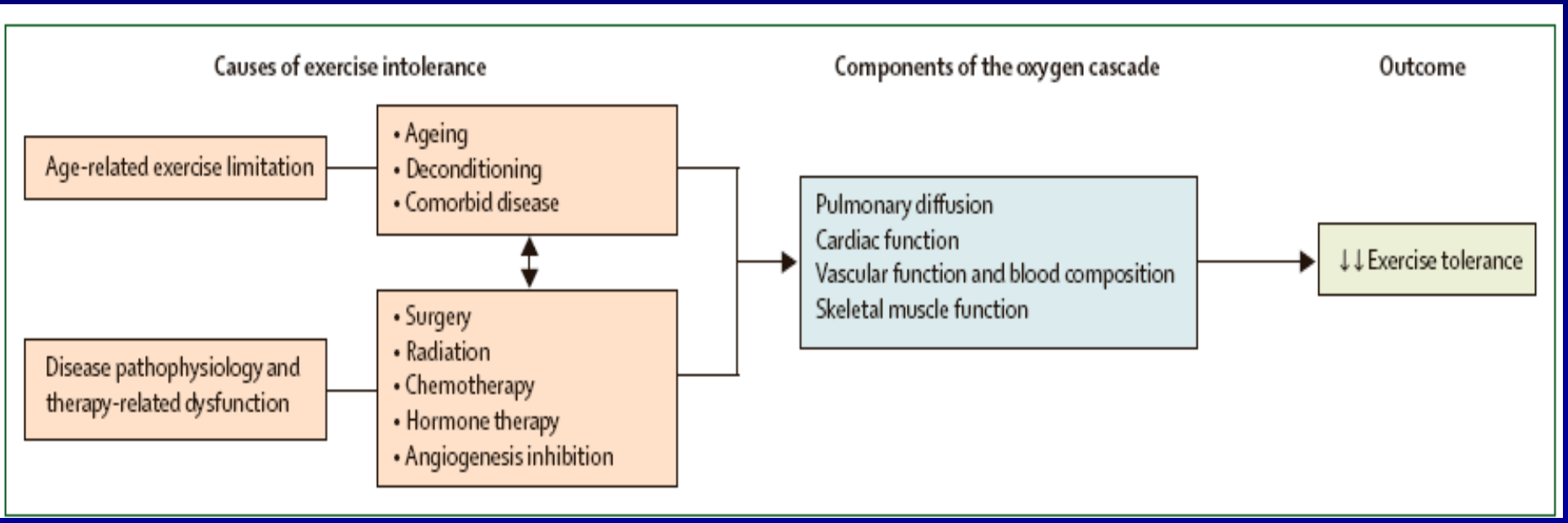
Patnaik et al. *Breast Ca Res*, 2011

Jones, AICR, 2011

The ‘Multiple-Hit’ hypothesis


Review

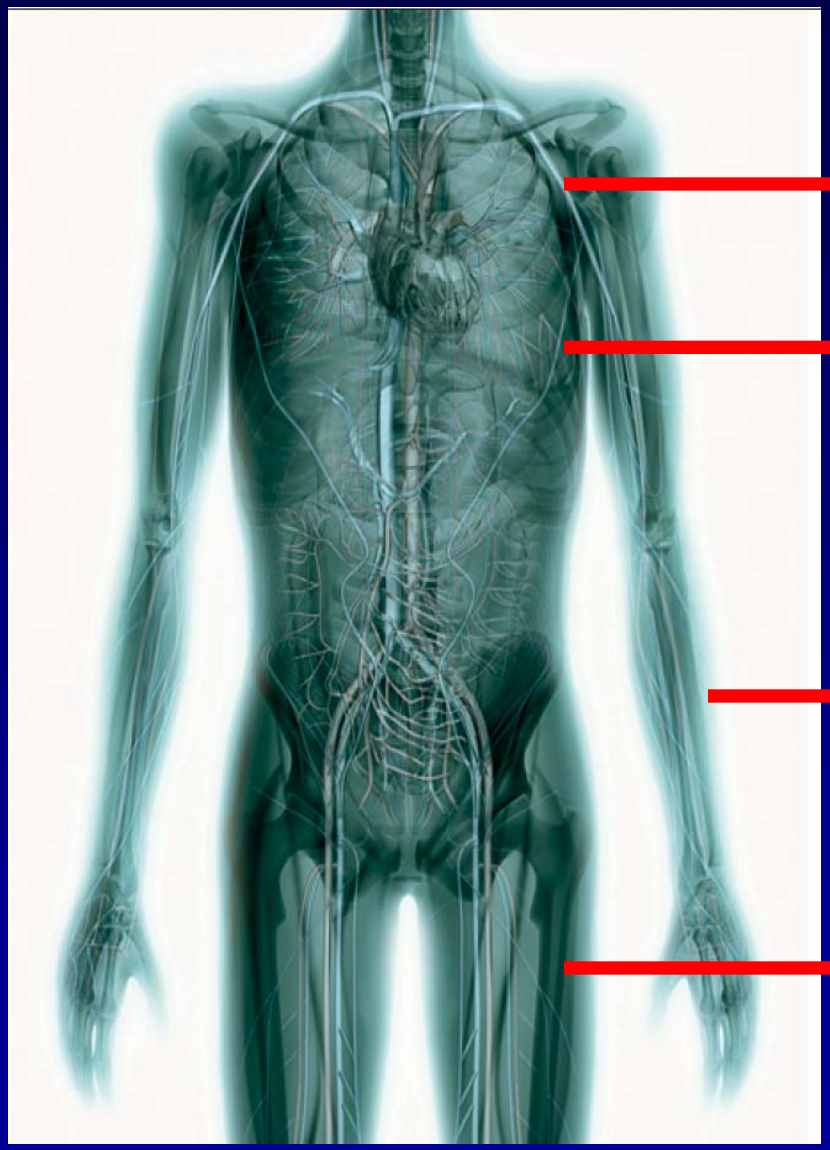
Exercise intolerance in cancer and the role of exercise therapy to reverse dysfunction



Jones et al. *Lancet Oncol, 2009*

Jones, AICR, 2011

What is cardiovascular reserve / exercise tolerance?



Pulmonary function (O_2 diffusion)

+

Cardiac function (Q, Hb concn, SpO_2)

+

Vascular compliance

+

Skeletal muscle function (oxidative capacity, fiber type distribution)

II

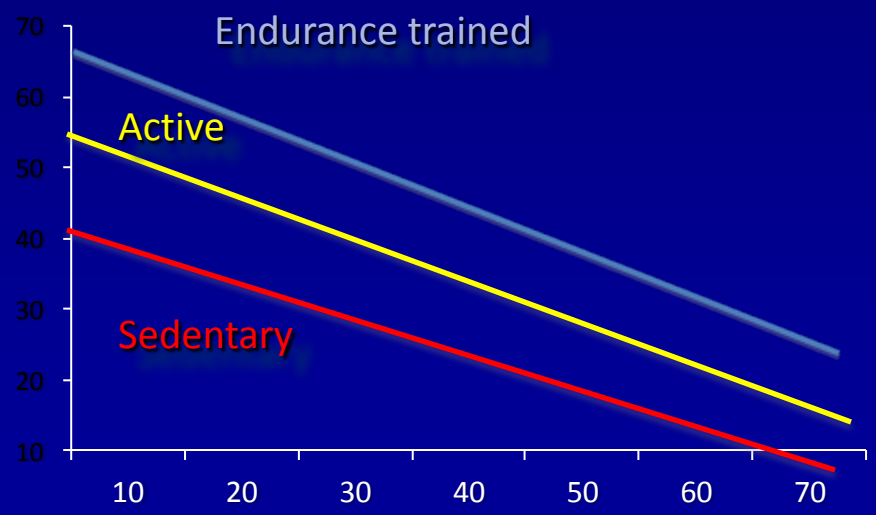
CV reserve / aerobic capacity

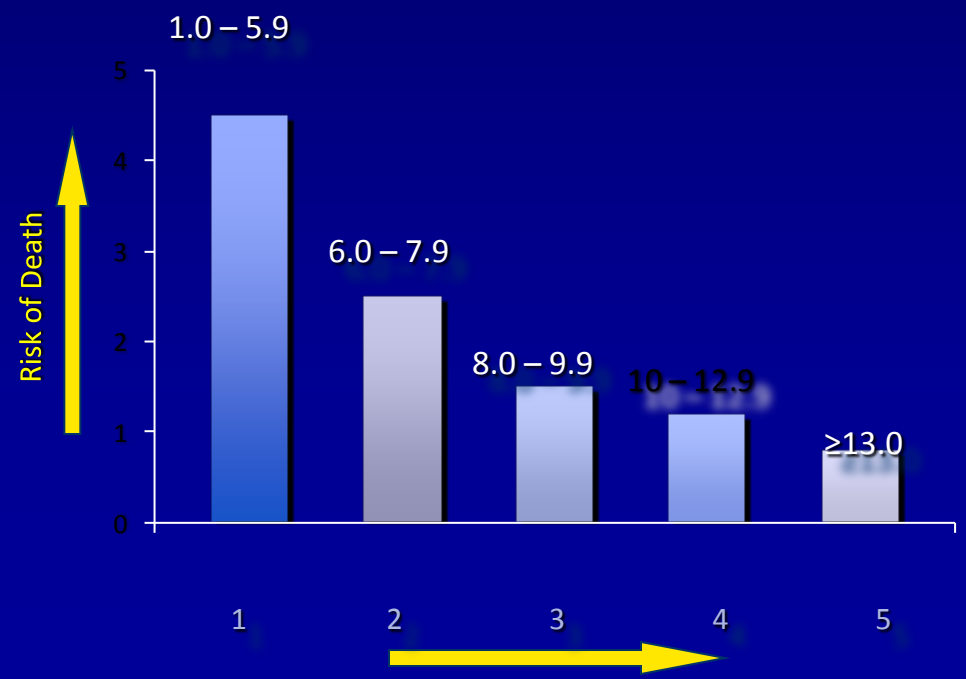
Jones et al. *Lancet Oncol*, 2009

Jones, AICR, 2011

Measurement of cardiovascular reserve

- Symptom-limited cardiopulmonary exercise test (CPET)
- Peak oxygen consumption (VO_{2peak} – $mL.kg.^{-1}min^{-1}$

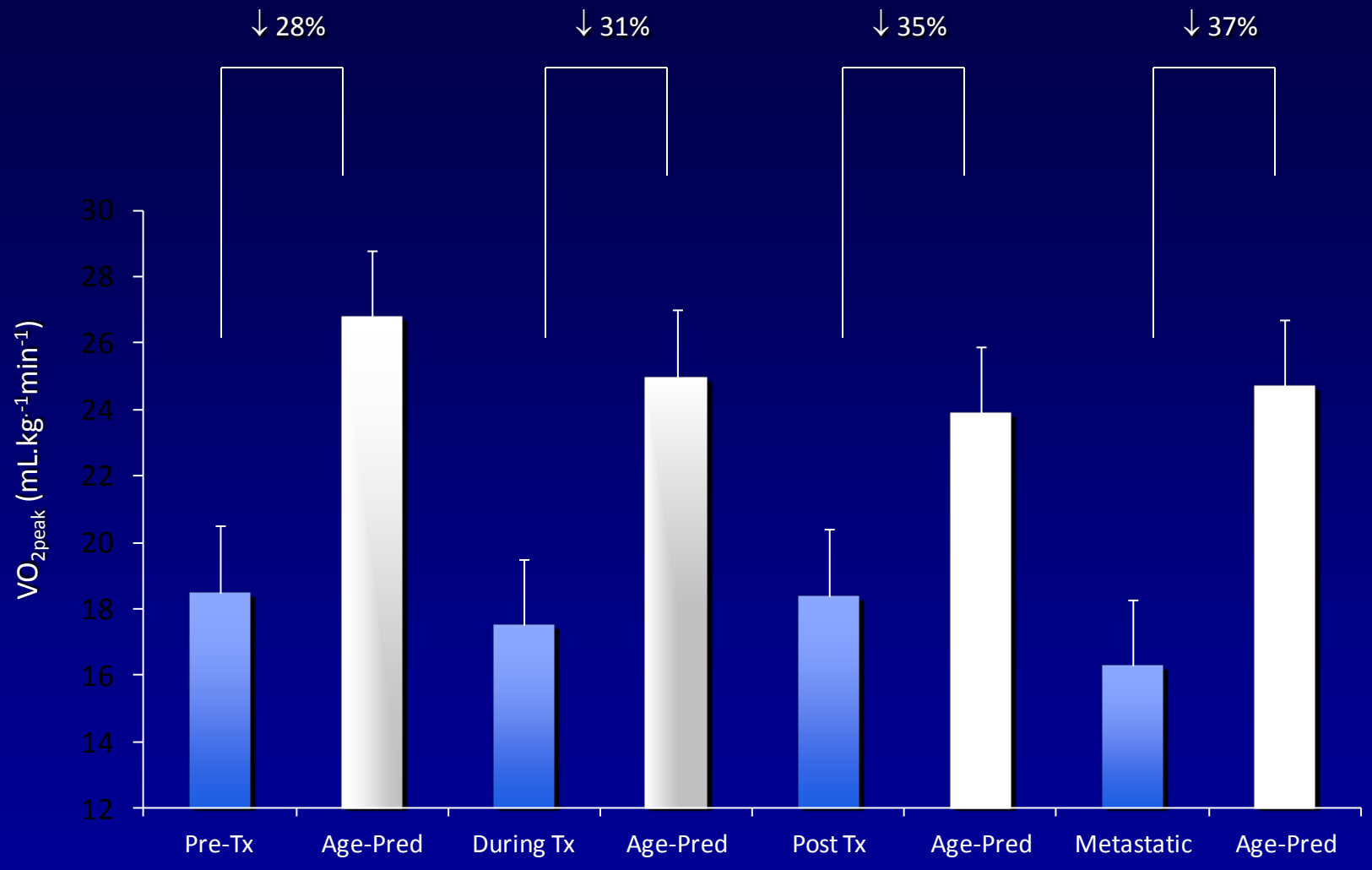




Jones et al. *Lancet Oncol*, 2008; Fitzgerald et al. *J Appl Physiol* 1997; Myers et al. *NEJM*, 2002

Jones, AICR, 2011

Impaired fitness across breast cancer continuum



Mean VO_{2peak} = 5.7 METs (Q1)!!

Jones et al. *J Clin Oncol* submitted

Jones, AICR, 2011

VO_{2peak} & all-cause mortality in operable NSCLC (n=398)

Original Article

Peak Oxygen Consumption and Long-Term All-Cause Mortality in Nonsmall Cell Lung Cancer

Lee W. Jones, PhD[1]; Dorothy Watson[2]; James E. Herndon, II, PhD[2]; Neil D. Eves, PhD[3]; Benjamin E. Haithcock[4]; Gregory Loewen, DO[5]; and Leslie Kohman, MD[6]

BACKGROUND: Identifying strong markers of prognosis is critical to optimize treatment and survival outcomes in patients with nonsmall cell lung cancer (NSCLC). The authors investigated the prognostic significance of preoperative cardiorespiratory fitness (peak oxygen consumption (VO_{2peak})) among operable candidates with NSCLC. **METHODS:** By using a prospective design, 398 patients with potentially resectable NSCLC enrolled in Cancer and Leukemia Group B 9238 were recruited between 1998 and 1998. Participants performed a cardiopulmonary exercise test to assess VO_{2peak} and were observed until death or June 2008. Cox proportional models were used to estimate the risk of all-cause mortality according to cardiorespiratory fitness category defined by VO_{2peak} tertiles (<0.96 of 0.96-1.29/ >1.29 L/min^{-1}) with adjustment for age, sex, and performance status. **RESULTS:** Median follow-up was 30.8 months; 294 deaths were reported during this period. Compared with patients achieving a VO_{2peak} <0.96 L/min^{-1}, the adjusted hazard ratio (HR) for all-cause mortality was 0.64 (95% confidence interval [CI], 0.46-0.88) for a VO_{2peak} of 0.96 to 1.29 L/min^{-1}, and 0.56 (95% CI, 0.39-0.80) for a VO_{2peak} of >1.29 L/min^{-1} (P_{trend} = .0037). The corresponding HRs for resected patients were 0.66 (95% CI, 0.46-0.95) and 0.59 (95% CI, 0.40-0.89) relative to the lowest VO_{2peak} category (P_{trend} = .0247), respectively. For nonresected patients, the HRs were 0.78 (95% CI, 0.34-1.79) and 0.39 (95% CI, 0.16-0.94) relative to the lowest category (P_{trend} = .0278). **CONCLUSIONS:** VO_{2peak} is a strong independent predictor of survival in NSCLC that may complement traditional markers of prognosis to improve risk stratification and prognostication. *Cancer* 2010;116:000–000. © 2010 American Cancer Society.

KEYWORDS: exercise, lung cancer, all-cause mortality, cardiorespiratory fitness, prognosis.

Lung cancer is the second most commonly diagnosed malignancy among American adults, accounting for approximately 15% of all cancer diagnoses.[1] An estimated 80% of lung cancer patients will be diagnosed with nonsmall cell lung cancer (NSCLC), and approximately 25% will present with early stage (operable) disease.[1] NSCLC continues to be the leading cause of cancer-related mortality, accounting for approximately 20% of all deaths.[1] Despite significant advancements in surgical procedures and introduction of postoperative chemotherapy, prognosis remains disappointing, with 5-year relative survival rates ranging from approximately 70% for patients with stage I disease to only approximately 25% for stage IIIA disease.[1] Furthermore, there is considerable survival variability within stage because of the heterogeneous features of disease pathophysiology and broad range of clinical comorbid conditions at presentation.[3,4] Thus, identifying accurate markers of prognosis to optimize treatment and survival outcomes in NSCLC is of major clinical importance.

Among the wide spectrum of predictive and prognostic markers that have been identified, performance status (PS) has consistently been demonstrated to be a strong, independent predictor of survival and a central component of practical prognostic models in NSCLC.[7] PS is an assessment of the patient's physical functioning and capability of self-care as recorded by oncology health professionals, but such scoring systems are subjective and have poor inter-rater reliability. Moreover, these instruments fail to characterize the degree or potential causes of physiologic limitation, assess symptom responses to exertion, or inform therapeutic intervention.[8]

Cancer March 00, 2010 1

	VO_{2peak} (mL·kg^{-1} min^{-1})			
	<13.9 (4 METS)	14.0 – 17.3 (>4 – 5 METS)	>17.3 (> 5 METS)	*P* for trend
<u>All Patients</u>				
Median, Mths	30.5	42.7	39.1	
5-year survival, %	30	34	36	
Adjusted*	Referent	0.79	0.76	0.0403

*Adjusted for age, gender, performance status, and FEV_1

Jones et al. *Cancer*, 2010

Jones, AICR, 2011

VO_{2peak} & all-cause mortality in metastatic breast cancer(n=52)

	VO_{2peak} ($L \cdot min^{-1}$)		
	≤1.09	>1.09	*P* for trend
Median, Mths	16 (7 to 27)	36 (24 to 57)	
Adjusted*	Referent	0.32	0.002

*adjusted for number of metastatic sites, age, and performance status

	VO_{2peak} ($mL \cdot Kg.^{-1} min^{-1}$)		
	≤15.4 (4.4 METS)	>15.4 (>4.4 METS)	*P* for trend
Median, Mths	22 (12 to 40)	29 (18 to 42)	
Adjusted*	Referent	0.59	0.141

*adjusted for number of metastatic sites, age, and performance status

Jones et al *J Clin Oncol,* submitted

Jones, AICR, 2011

Treatment vs. prevention of injury?

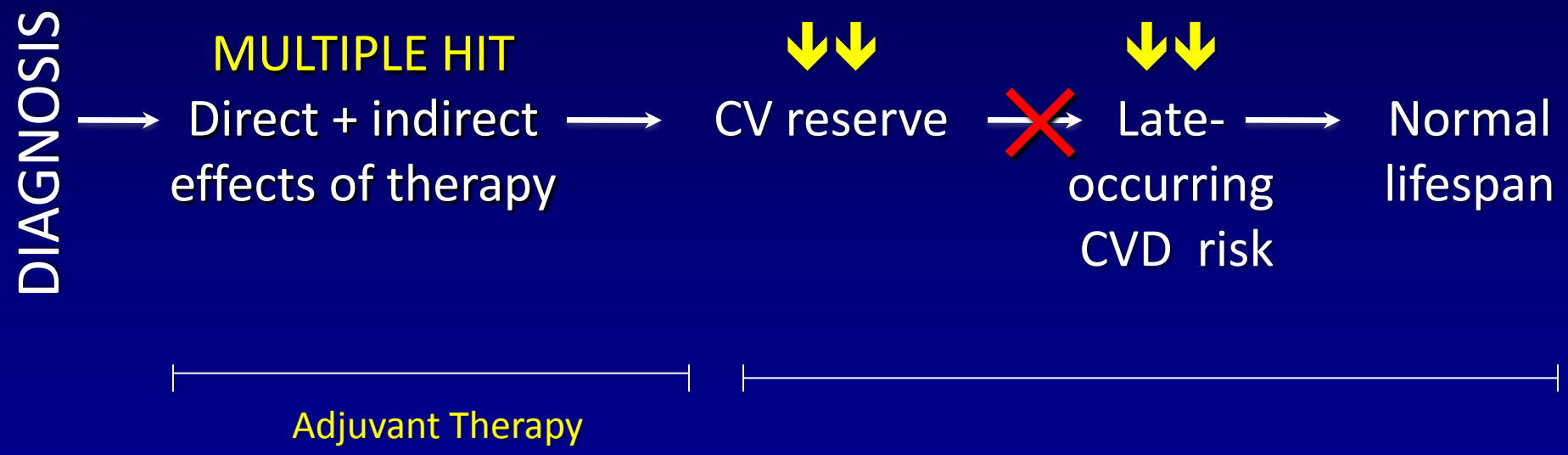
DIAGNOSIS → MULTIPLE HIT Direct + indirect effects of therapy → ↓↓ CV reserve → ↑↑ Late-occurring CVD risk → ↑↑ Premature death

Adjuvant Therapy

Post Adjuvant Therapy (Recovery / Survivorship)

Jones, AICR, 2011

Treatment of injury



Jones, AICR, 2011

Example trial: Courneya et al. *J Clin Oncol*, 2003

Randomized Controlled Trial of Exercise Training in Postmenopausal Breast Cancer Survivors: Cardiopulmonary and Quality of Life Outcomes

By Kerry S. Courneya, John R. Mackey, Gordon J. Bell, Lee W. Jones, Catherine J. Field, and Adrian S. Fairey

Purpose: To determine the effects of exercise training on cardiopulmonary function and quality of life (QOL) in postmenopausal breast cancer survivors who had completed surgery, radiotherapy, and/or chemotherapy with or without current hormone therapy use.

Methods: Fifty-three postmenopausal breast cancer survivors were randomly assigned to an exercise (n = 25) or control (n = 28) group. The exercise group trained on cycle ergometers three times per week for 15 weeks at a power output that elicited the ventilatory equivalent for carbon dioxide. The control group did not train. The primary outcomes were changes in peak oxygen consumption and overall QOL from baseline to postintervention. Peak oxygen consumption was assessed by a graded exercise test using gas exchange analysis. Overall QOL was assessed by the Functional Assessment of Cancer Therapy–Breast scale.

Results: Fifty-two participants completed the trial. The exercise group completed 92.4% of the exercise sessions. Baseline values for peak oxygen consumption (P = .354) and overall QOL (P = .286) did not differ between groups. Peak oxygen consumption increased by 0.24 L/min in the exercise group, whereas it decreased by 0.05 L/min in the control group (mean difference, 0.29 L/min; 95% confidence interval [CI], 0.18 to 0.40; P < .001). Overall QOL increased by 9.1 points in the exercise group compared with 0.3 points in the control group (mean difference, 8.8 points; 95% CI, 3.6 to 14.0; P = .001). Pearson correlations indicated that change in peak oxygen consumption correlated with change in overall QOL (r = 0.43; P < .01).

Conclusion: Exercise training had beneficial effects on cardiopulmonary function and QOL in postmenopausal breast cancer survivors.

J Clin Oncol 21:1660–1668. © 2003 by American Society of Clinical Oncology.

BREAST CANCER is a prevalent disease[1] that requires intensive and prolonged treatment.[2] Cardiopulmonary capacity may be compromised in breast cancer survivors because of the pathology of the disease, therapeutic regimens, and weight gain and inactivity secondary to treatment. The reduction in cardiopulmonary capacity may lead to reductions in quality of life (QOL)[3,4] or premature death.[5,7]

Research has provided preliminary evidence for the safety, feasibility, and efficacy of exercise training in breast cancer survivors.[8,9] Few studies, however, have been randomized controlled trials.[8] Overall, little is known about the impact of exercise training on cardiopulmonary function and QOL in breast cancer survivors. The role of exercise training in recovery after treatments may be particularly important because not all breast cancer survivors seem willing or able to tolerate exercise during adjuvant therapies.[10] However, QOL may be still be compromised in the months and years after treatment.[11]

The Exhibitionists Exercise for Health After Breast Cancer (EEHAB) trial was a randomized controlled trial designed to determine the effects of supervised exercise training on cardiopulmonary, QOL, and biologic outcomes in postmenopausal breast cancer survivors who had completed surgery, radiotherapy, and/or chemotherapy with or without current hormone therapy use. Here we report the effects of exercise training on the cardiopulmonary and QOL outcomes. The primary outcomes were changes in peak oxygen consumption and overall QOL between baseline and postintervention. We hypothesized that exercise training would have beneficial effects on both of these outcomes. We also hypothesized that the changes in cardiopulmonary function would be correlated with the changes in QOL. Effects on the biologic outcomes will be reported separately.

METHODS

Setting and Participants:

The trial was conducted at the Cross Cancer Institute (CCI) and University of Alberta (Edmonton, Alberta, Canada). The Alberta Cancer Board and the University of Alberta approved the trial. Written informed consent was obtained for all procedures.

Eligibility criteria included histologically confirmed early-stage breast cancer with no evidence of recurrent or progressive disease; diagnosis between January 1999 and June 2000; completed surgery, radiotherapy, and/or chemotherapy with or without current hormone therapy use; postmenopausal status (not experiencing menstrual periods for previous 12

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1660

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Stage I-III

Completed therapy

Post-menopausal

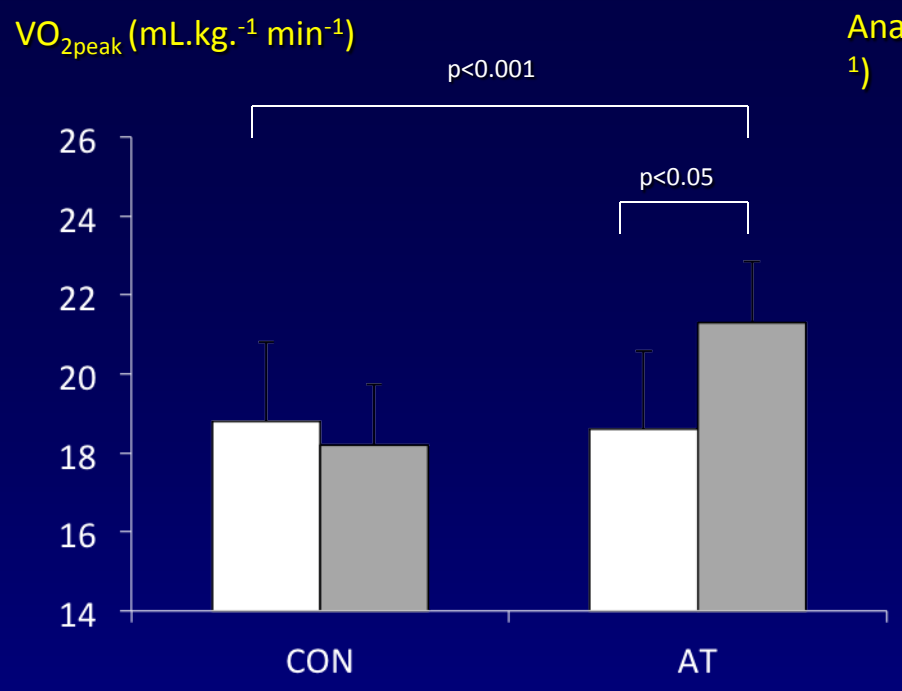
n=53

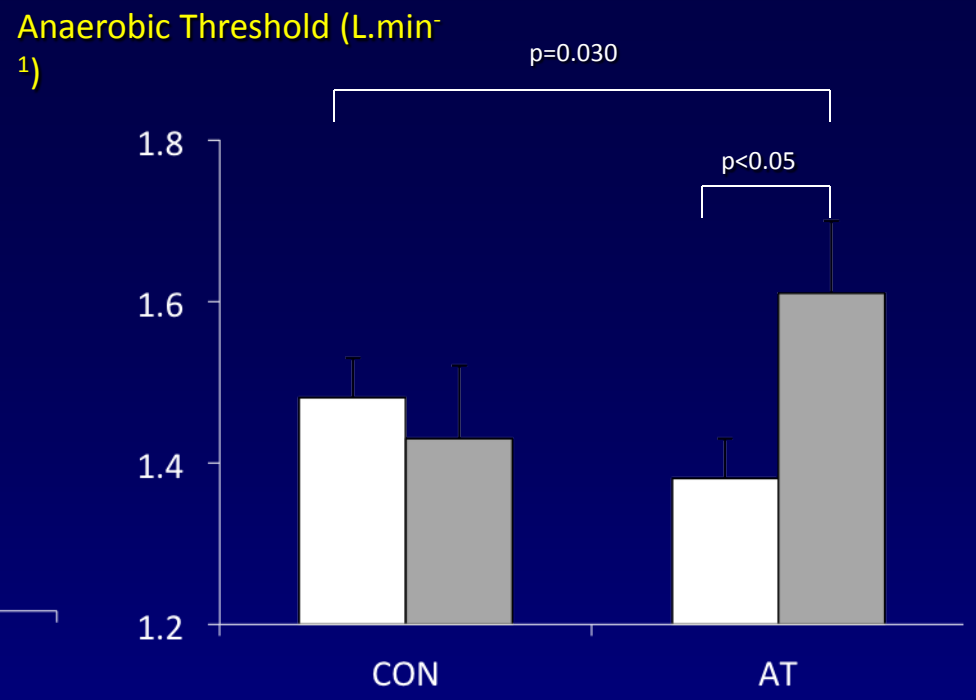
Wait-List Control (n=28)

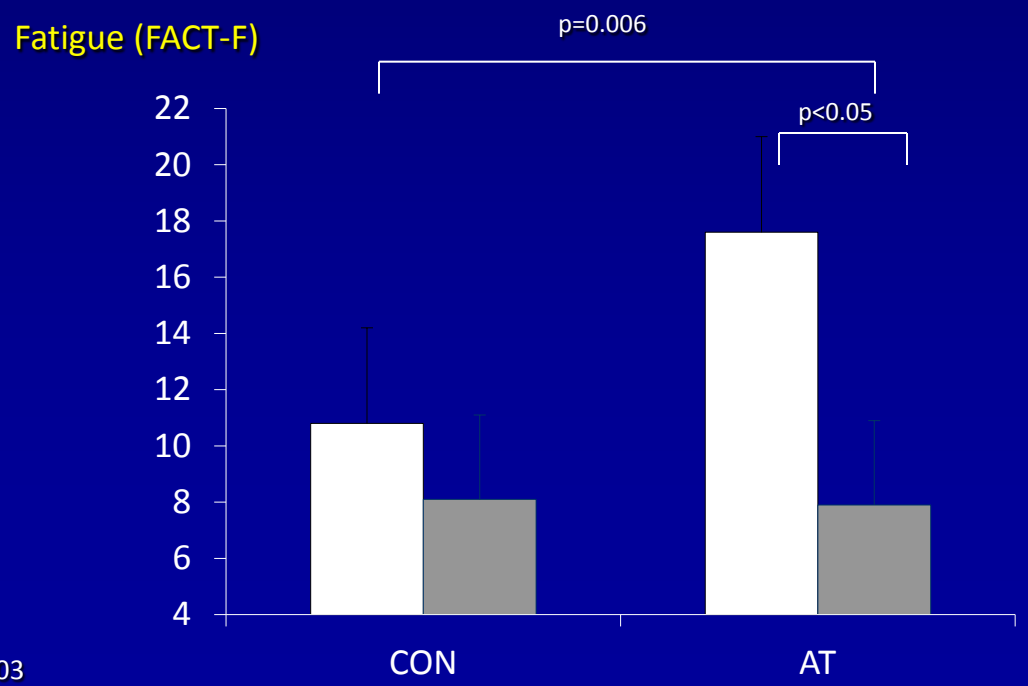
Provided with exercise program >study

Supervised Aerobic Training (n=25)

Cycle ergometry, @ 75% VO_{2peak} 20-45 mins/session, 3x/wk for 15 wks







Courneya et al. *J Clin Oncol*, 2003

Jones, AICR, 2011

Efficacy of aerobic training post therapy: Summary

- ~17 studies
- Majority tested aerobic-based interventions
  - Cycle ergometry/treadmill walking
  - 3d.wk for 6-24 weeks, moderate intensity
- Adherence: 88 ± 12; Loss-to-follow-up: 11 ± 14
- Few SAEs (few studies monitor / report SAEs)
- ↑ VO_{2peak}, ↑QOL & ↓fatigue
- Strong preliminary evidence
- 2nd generation trials underway (optimal exercise px)

Jones et al. *C Med Assoc J*, submitted

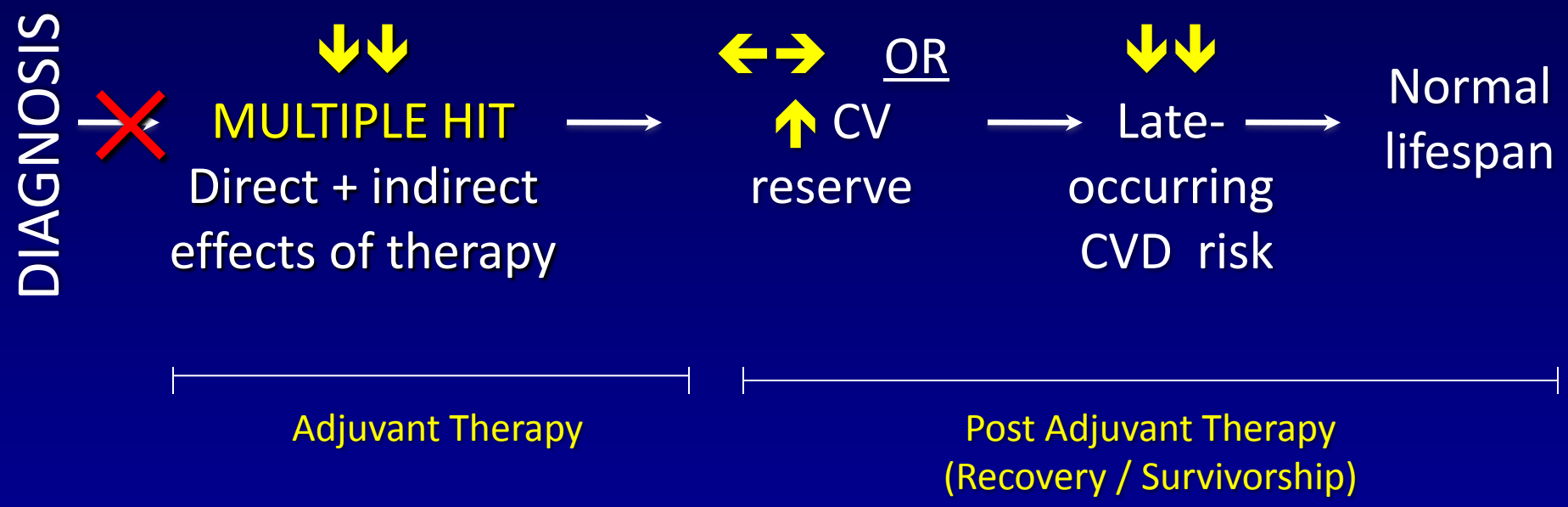
Jones, AICR, 2011

Jones Lab: Ongoing RCTs

Trial	Funding Source	Population	Design	Intervention	Length	Status
1. LUNGEVITY	NIH (R01)	160 Early NSCLC post therapy	4 Arm RCT	1. AT 2. RT 3. AT +RT 4. Att. Con	16 weeks	50 patients randomized
2. EXCITE	NIH (R01)	174 Early breast cancer post therapy	3 Arm RCT	1. Moderate AT 2. High AT 3. Att. Con	16 weeks	42 patients randomized
3. Exercise - ED	NIH (R21)	50 Post-Sx prostate cancer	2 Arm RCT	1. High - moderate AT 2. Control	24 weeks	32 patients randomized
4. Exercise - CRC	NIH (U54)	120 Post-Tx CRC	4 Arm RCT	1. AT 2. Metformin 3. AT + Metformin 4. Control	24 weeks	Nov, 2011

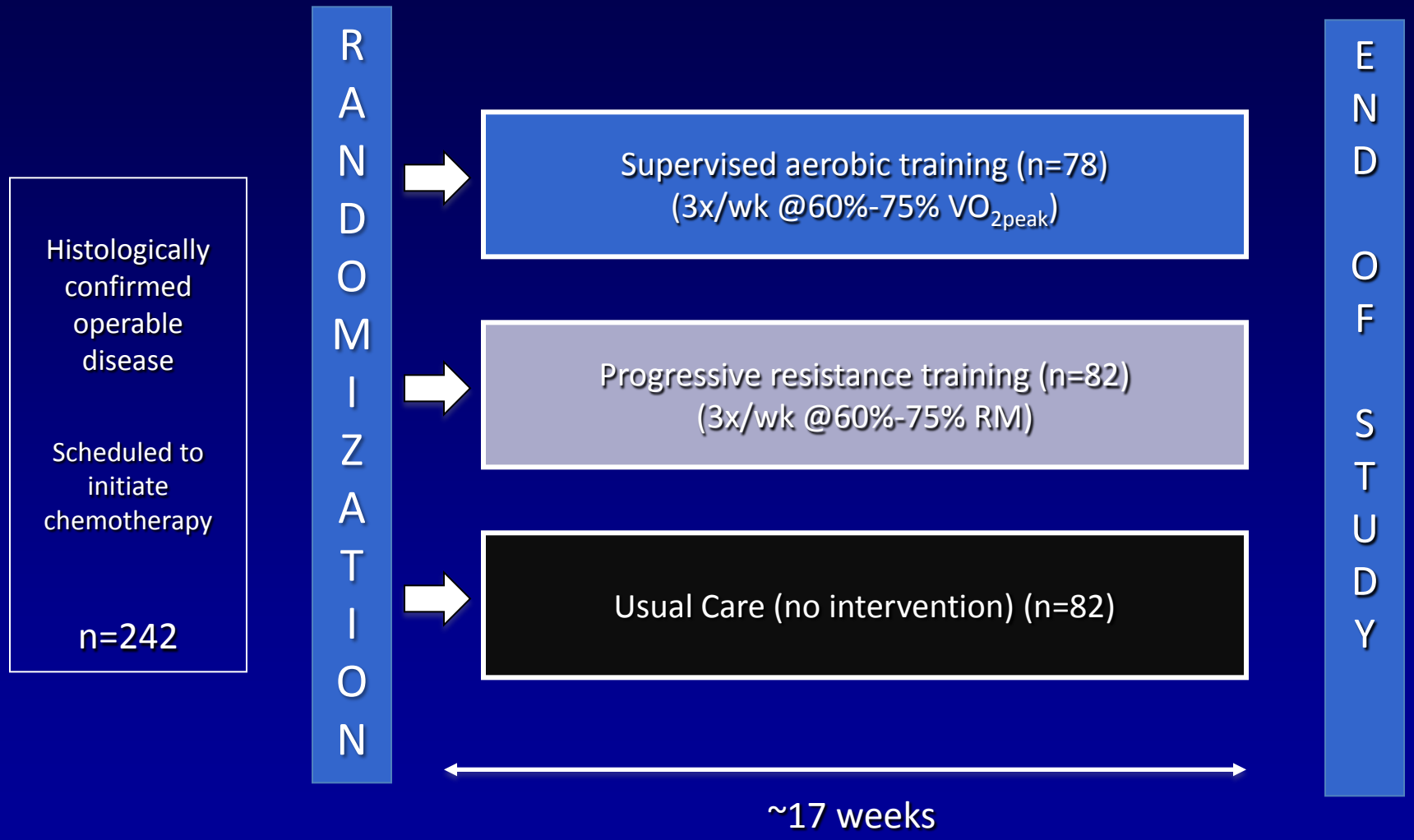
Jones, AICR, 2011

Prevention of injury?



Jones, AICR, 2011

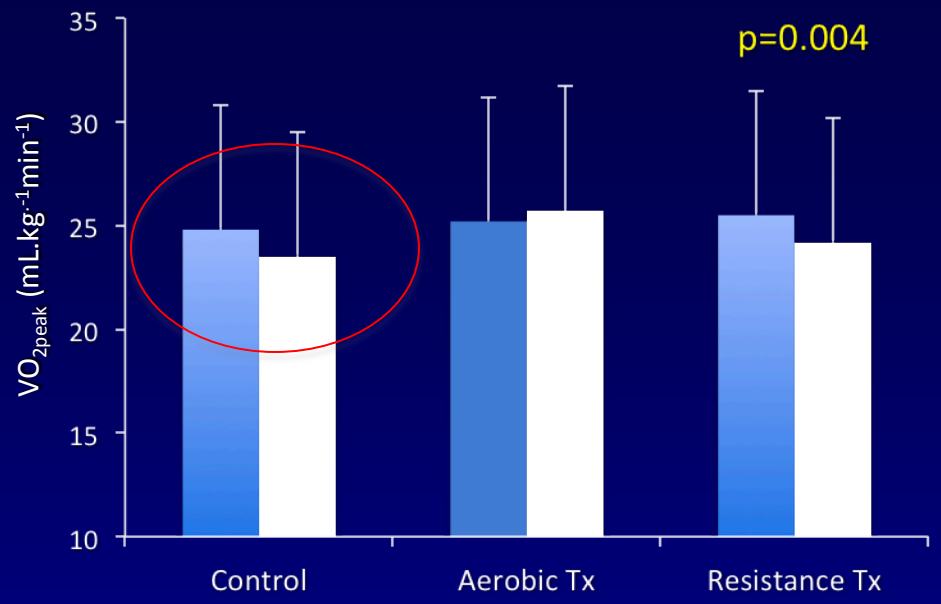
Example trial: Courneya et al. *J Clin Oncol*, 2007



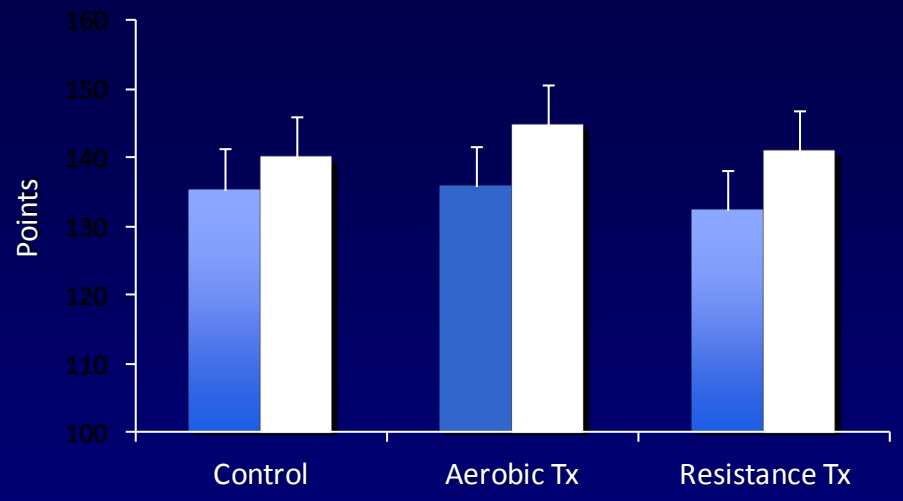
Courneya et al. *J Clin Oncol*, 2007

Jones, AICR, 2011

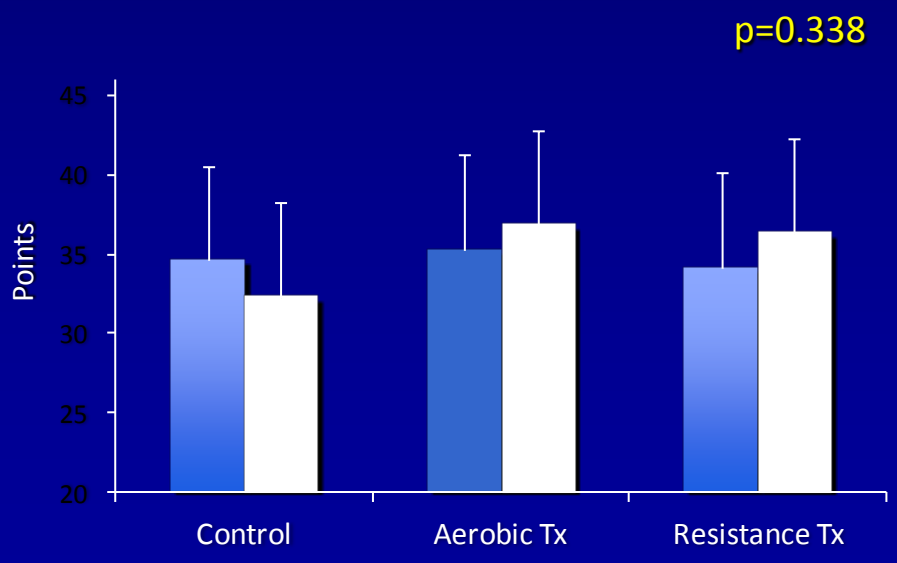
Aerobic capacity



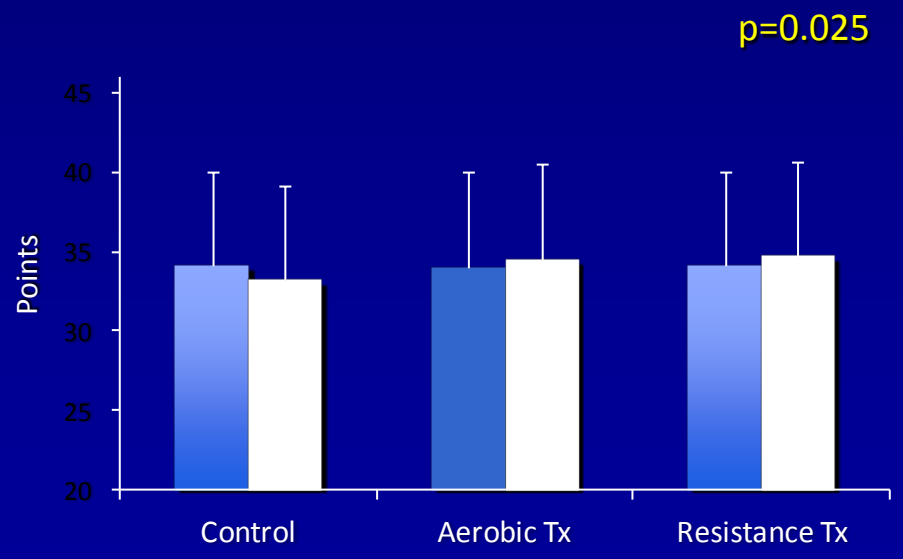
QOL



Fatigue



Self-esteem



Courneya et al. *J Clin Oncol*, 2007

Jones, AICR, 2011

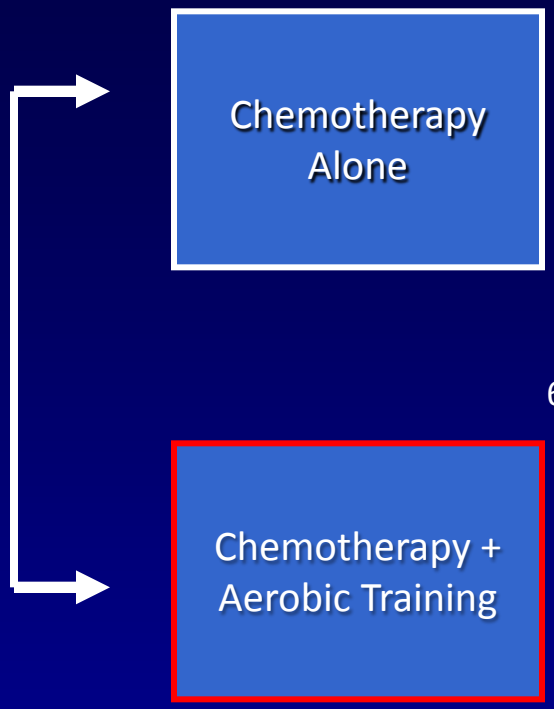
Breast cancer neoadjuvant trial

Tumors >1.5 cm

LVEF >50%

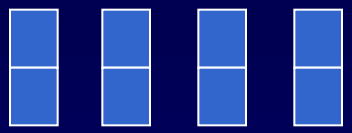
KPS >70%

n=20



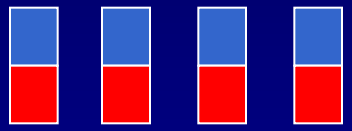
4 x AC

60/600 mg/m^2



4 x AC + AT

60/600 mg/m^2 / cycle ergomtery (3x.wk, 60% - 100% VO_{2peak} for 12 wks)

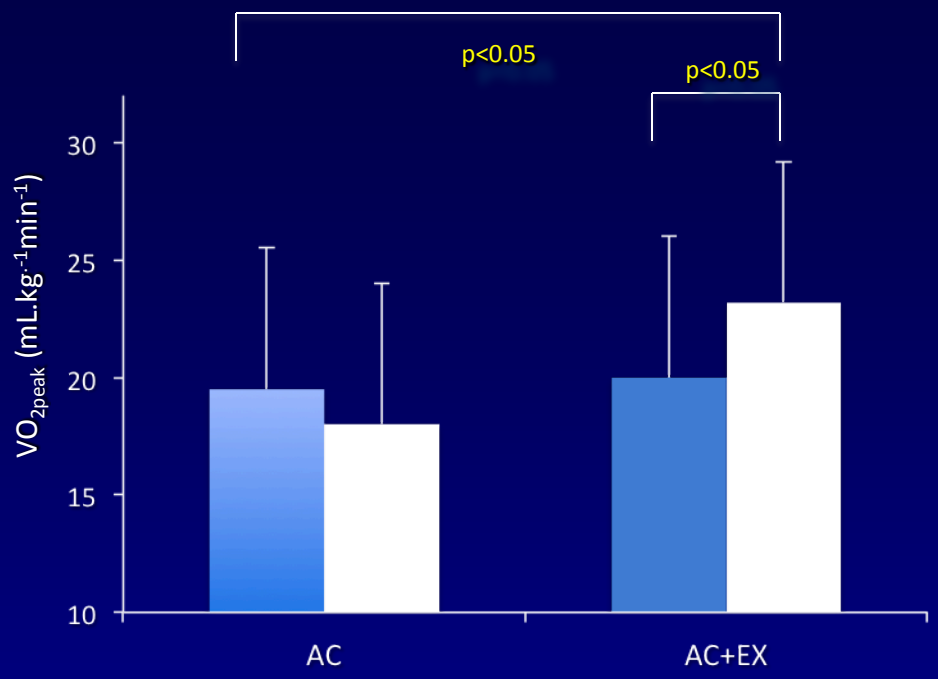


- Aerobic capacity (CPET; VO_{2peak})
- LV Function (2-D echo)
- Endothelial function (flow-mediated dilatation)
- Patient-reported outcomes

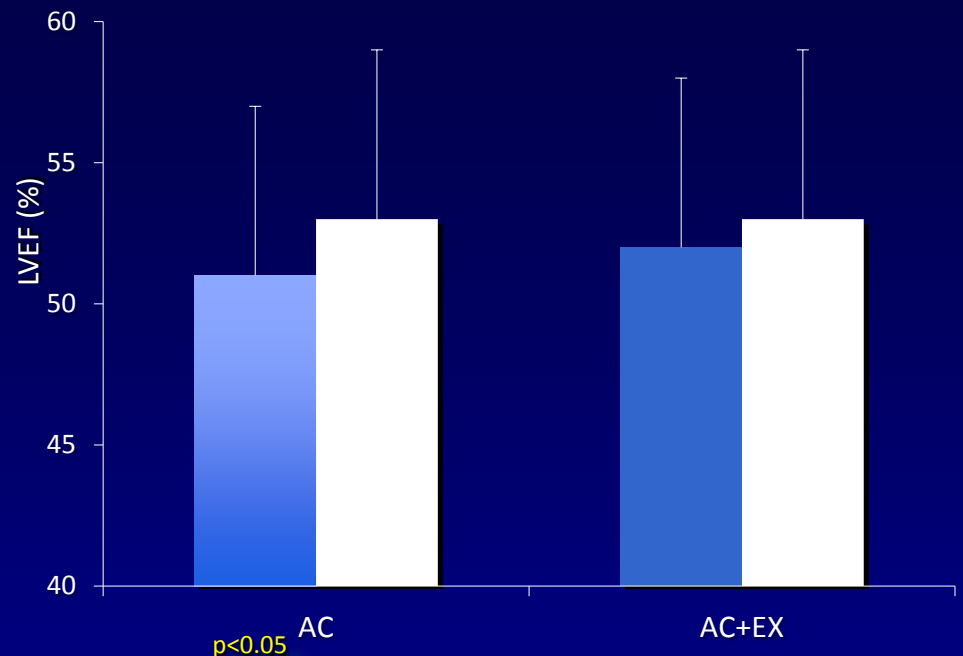
Jones et al. *in prep*

Jones, AICR, 2011

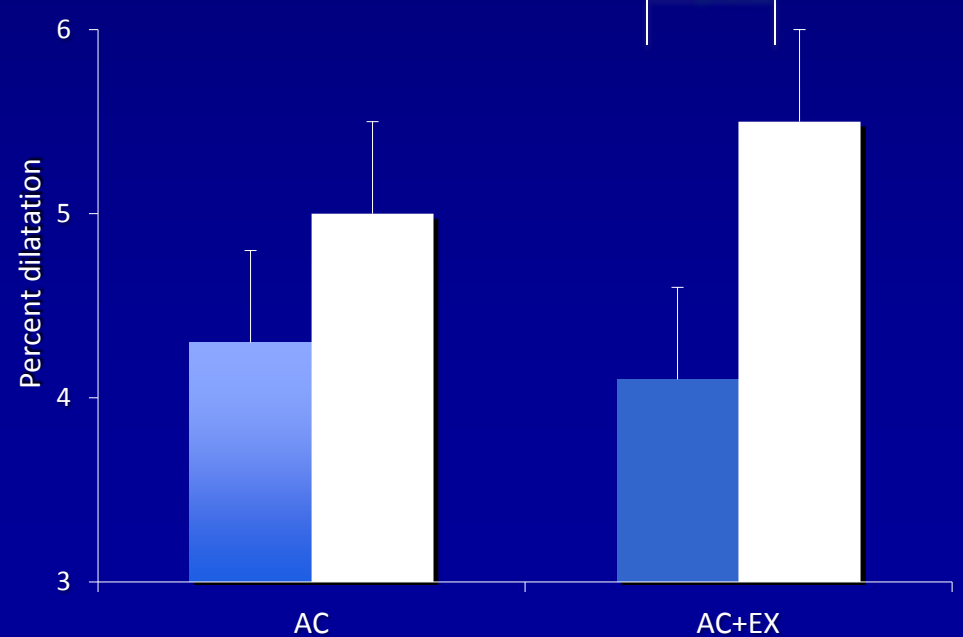
Aerobic capacity



Cardiac function (ejection fraction)



Endothelial function



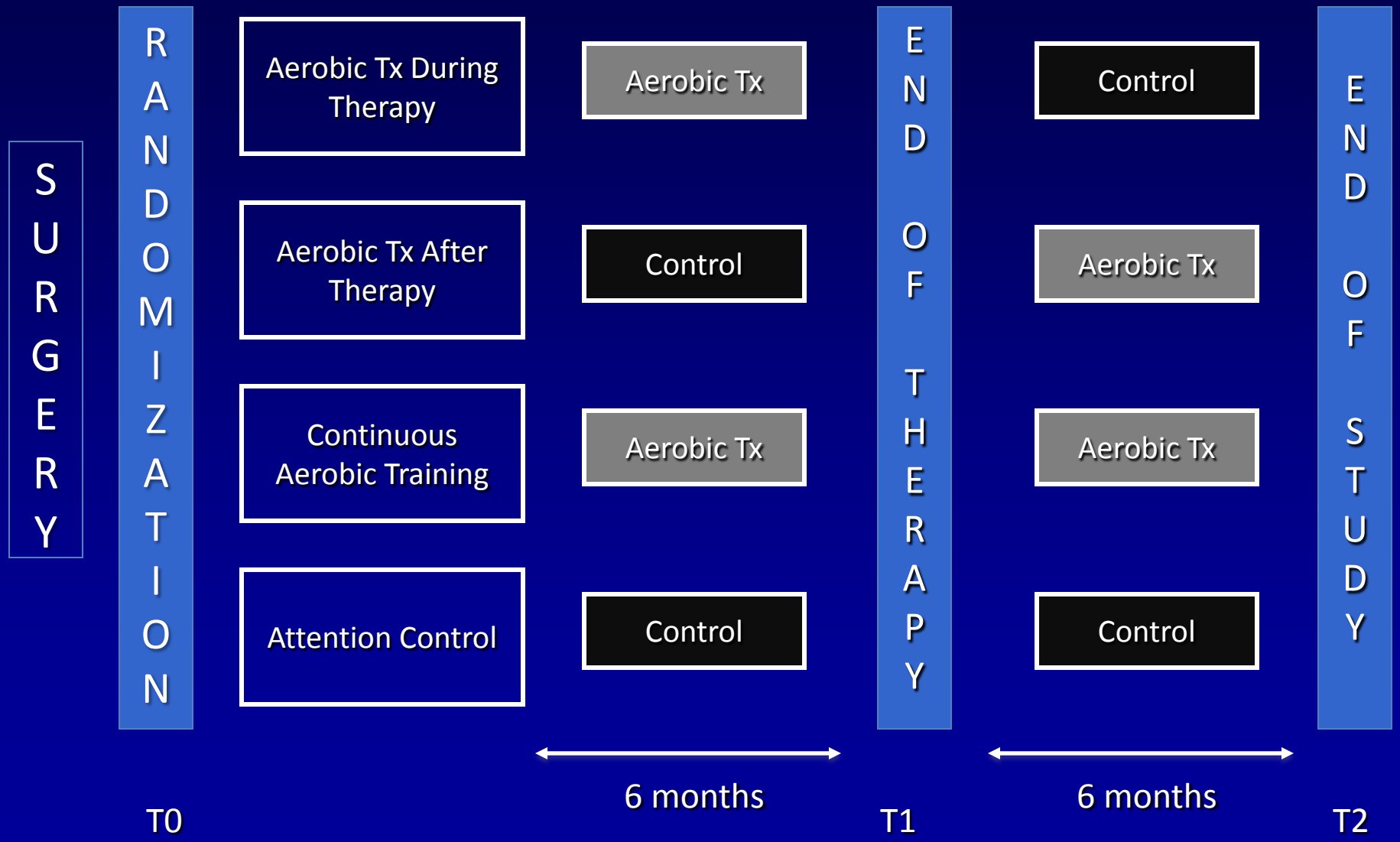
Jones et al. *in prep*

Efficacy of aerobic training during therapy: Summary

- ~20 studies (breast Ca, small sample sizes)
- Majority tested aerobic-based interventions
  - Cycle ergometry/treadmill walking
  - 3d.wk for 6-24 weeks, moderate intensity
- Adherence: 84 ± 15; Loss-to-follow-up: 13 ± 13
- Few SAEs (few studies monitor / report SAEs)
- ↑ VO_{2peak}, QOL & ↓fatigue (more equivocal)
- Promising evidence
- Larger, more diverse RCTs (other Ca's; novel tx)

Jones et al. *C Med Assoc J*, submitted

Timing of exercise rehab: during vs. after therapy?



Jones, AICR, 2011

Exercise / physical activity and cancer-specific mortality in cancer survivors

Jones, AICR, 2011

Physical activity and prognosis in cancer survivors

ORIGINAL CONTRIBUTION

Physical Activity and Survival After Breast Cancer Diagnosis

Michelle D. Holmes, MD, DrPH
Wendy Y. Chen, MD
Diane Feskanich, ScD
Candace H. Kroenke, ScD
Graham A. Colditz, MD, DrPH

Context Physical activity has been shown to decrease the incidence of breast cancer, but the effect on recurrence or survival after a breast cancer diagnosis is not known.

Objective To determine whether physical activity among women with breast cancer decreases their risk of death from breast cancer compared with more sedentary women.

Design, Setting, and Participants Prospective observational study based on responses from 2987 female registered nurses in the Nurses' Health Study who were diagnosed with stage I, II, or III breast cancer between 1984 and 1998 and who were followed up until death or June 2002, whichever came first.

Main Outcome Measure Breast cancer mortality risk according to physical activity category (<3, 3-8.9, 9-14.9, 15-29.9, or ≥24 metabolic equivalent task (MET) hours per week).

Results Compared with women who engaged in less than 3 MET-hours per week of physical activity, the adjusted relative risk (RR) of death from breast cancer was 0.80 (95% confidence interval [CI], 0.60-1.06) for 3 to 8.9 MET-hours per week; 0.50 (95% CI, 0.31-0.82) for 9 to 14.9 MET-hours per week; 0.56 (95% CI, 0.38-0.84) for 15 to 23.9 MET-hours per week; and 0.60 (95% CI, 0.40-0.89) for 24 or more MET-hours per week (P for trend = .004). Three MET-hours is equivalent to walking at an average pace of 2 to 2.9 mph for 1 hour. The benefit of physical activity was particularly apparent among women with hormone-responsive tumors. The RR of breast cancer death for women with hormone-responsive tumors who engaged in 9 or more MET-hours per week of activity compared with women with hormone-responsive tumors who engaged in less than 3 MET-hours per week was 0.50 (95% CI, 0.34-0.74). Compared with women who engaged in less than 3 MET-hours per week of activity, the absolute unadjusted mortality risk reduction was 6% at 10 years for women who engaged in 9 or more MET-hours per week.

Conclusions Physical activity after a breast cancer diagnosis may reduce the risk of death from the disease. The greatest benefit occurred in women who performed the equivalent of walking 3 to 5 hours per week at an average pace, with little evidence of a dose-relation between increased benefit and greater energy expenditure. Women with breast cancer who follow US physical activity recommendations may improve their survival.

JAMA. 2005;293:2479-2486 www.jama.com

Women engaging in ≥9 MET (hrs.wk) (30 mins walking, 5d/wk) ~50% ↓ in BC-mortality & ~30% ↓ all-cause vs. inactive women

Holmes et al. *JAMA* 2005;293:2479-86

ORIGINAL INVESTIGATION

Physical Activity and Male Colorectal Cancer Survival

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Background: Although physically active individuals have a lower risk of developing colorectal cancer, few studies have examined whether exercise benefits colorectal cancer survivors.

Methods: Derived from the Health Professionals Follow-up Study, we studied colorectal cancer–specific and overall mortality in a cohort of 668 men with a history of stage I to stage III colorectal cancer according to predefined physical activity categories after diagnosis. To minimize bias by occult recurrences, we excluded men who died within 6 months of their postdiagnosis physical activity assessment.

Results: In a cohort of men with colorectal cancer and no apparent metastases at diagnosis, 50.4% exercised at least 18 metabolic equivalent task (MET) hours per week. Increased physical activity was significantly associated with improved colorectal cancer–specific mortality (P = .002 for trend) and overall mortality (P < .001 for trend). Men who engaged in more than 27 MET-hours per week of physical activity had an adjusted hazard ratio for colorectal cancer–specific mortality of 0.47 (95% confidence interval, 0.24–0.92) compared with men who engaged in 3 or less MET-hours per week of physical activity. The apparent benefit of physical activity was seen regardless of age, disease stage, body mass index, diagnosis year, tumor location, and prediagnosis physical activity.

Conclusion: In a large cohort of men with a history of nonmetastatic colorectal cancer, more physical activity was associated with a lower risk of colorectal cancer–specific and overall mortality.

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Despite appreciable advances in screening and treatment of colorectal cancer, more than 148 000 individuals in the United States will be newly diagnosed as having colorectal cancer each year, and almost 57 000 annually will die of the disease.[1] A host of modifiable factors have been associated with influencing the likelihood of developing the disease.[2] A recent meta-analysis[3] of 52 observational studies found an inverse relationship between physical activity and colon cancer development, with an overall relative risk of 0.76 (95% confidence interval [CI], 0.72-0.81).

See also pages 2106, 2109, and 2116

Although there is little debate about the benefit of physical activity in preventing the development of colorectal cancer, the role of physical activity in colorectal cancer survivors is less certain. Recently, findings from several studies suggest that prediagnosis physical activity[4] or postdiagnosis physical activity[5,6] reduces the risk of cancer recurrence and improves mortality in colorectal cancer survivors. However, because randomized data are unavailable, further studies with prospectively collected data, comprehensive follow-up, and postdiagnosis physical activity levels are needed.

See Invited Commentary on page 2124

We used the Health Professionals Follow-up Study (HPFS) to test the association between physical activity and colorectal cancer mortality. This study comprised a large prospective cohort of more than 30 000 men who have been diagnosed as having colorectal cancer.

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Individuals engaging in ≥18 MET (hrs.wk) (60 mins walking, 5d/wk) ~50% ↓ in CRC-mortality & ~30% ↓ all-cause vs. inactive individuals

Meyerhardt et al. *Arch Intern Med* 2009; *J Clin Oncol* 2006; *Clin Cancer Res*, 2009

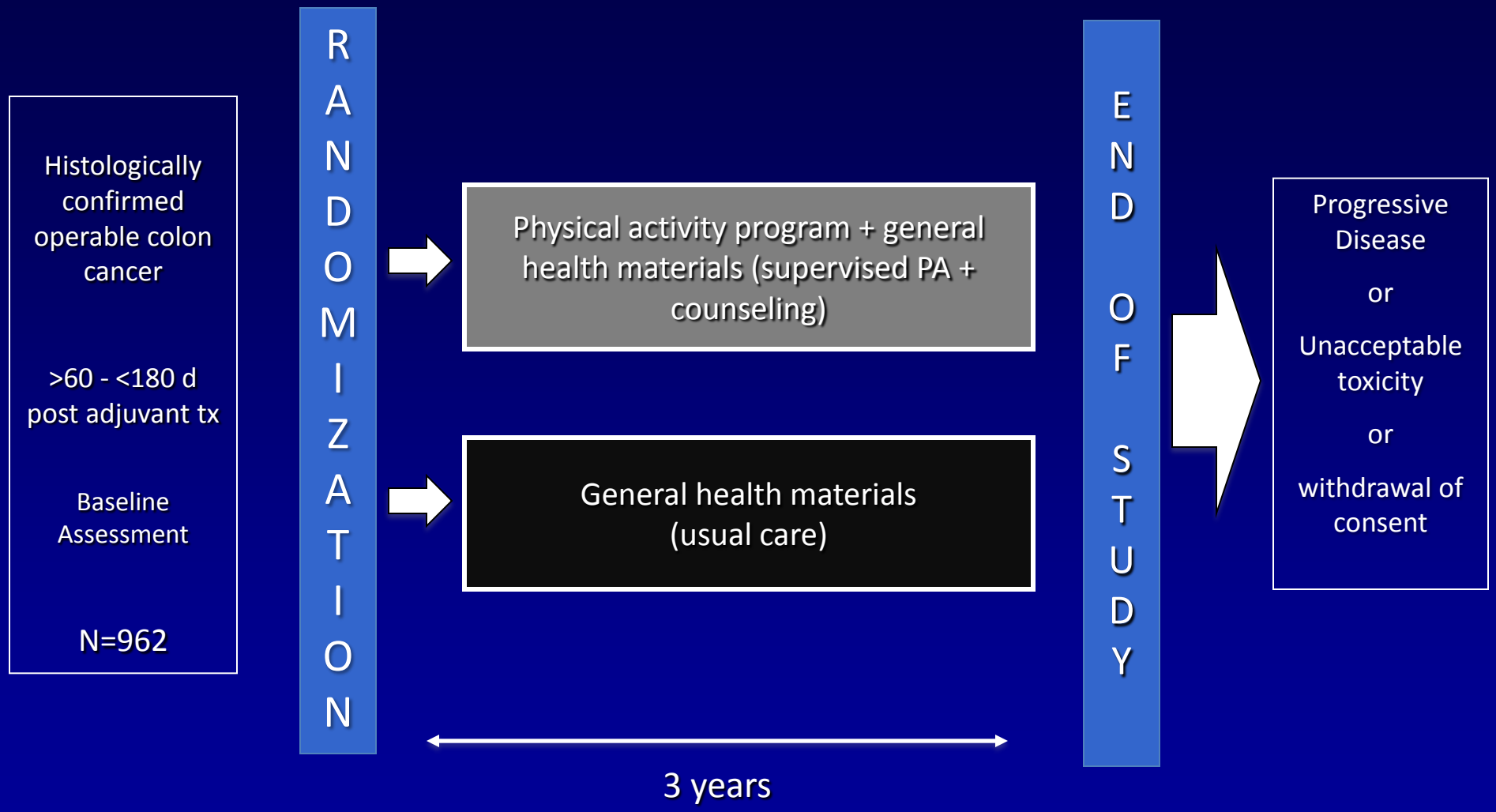
Jones, AICR, 2011

Physical activity and prognosis: Summary

- No RCTs of exercise on disease outcomes following a cancer diagnosis
- 13 observational studies self-reported exercise and cancer-specific and all-cause mortality
- 85% reported significant inverse relationship with risk reduction of 15% to 61% (cancer-specific) and 18% to 67% (all-cause mortality)
- 'Dose-response' reported in 6 studies
- Exercise volume from >2 $hrs.wk^{-1}$ to >7.5 $hrs.wk^{-1}$ of moderate-intensity exercise

Jones et al. *CMAJ*, submitted

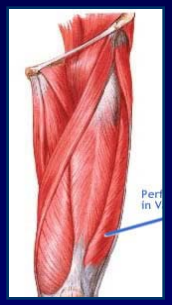
CHALLENGE Trial (Courneya et al. *Curr Oncol*, 2008)



- Primary: disease-free survival
- Secondary: PROs, functional capacity, etc.

Jones, AICR, 2011

Mechanisms of action



Changes in the host environment

Metabolic steroid hormones

Cytokines / angiogenic factors

Immunity

Sex steroid hormones

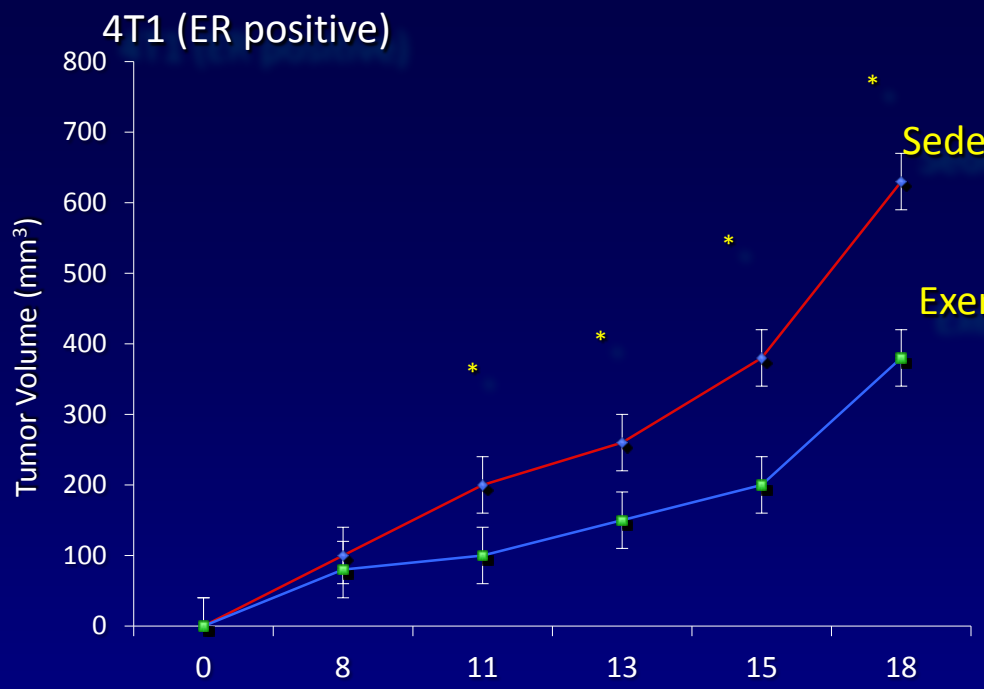
Oxidative damage

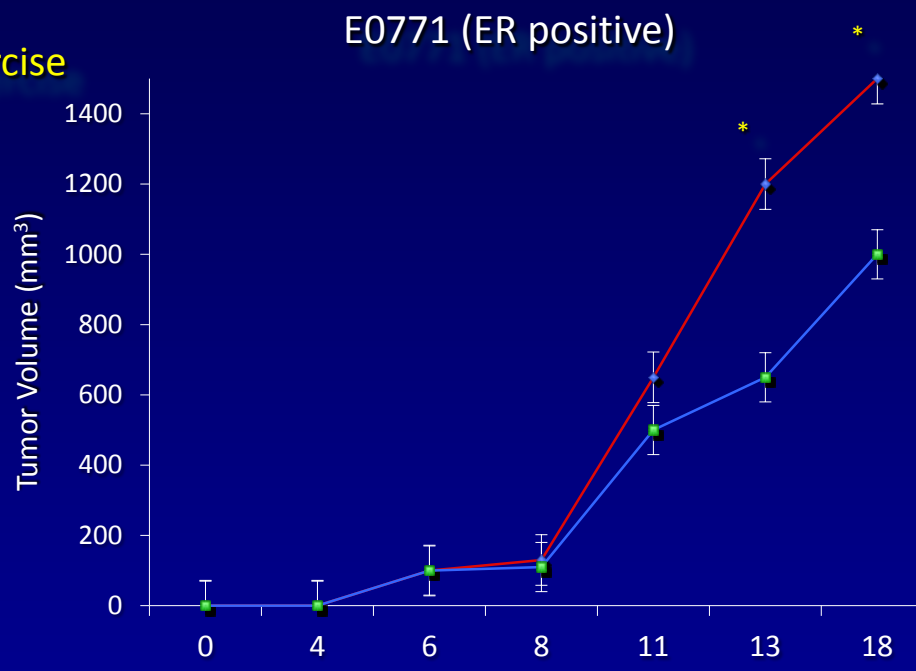
Modulation of the tumor mircoenvironment (seed) *and* mircoenvironment of distant organs (soil)

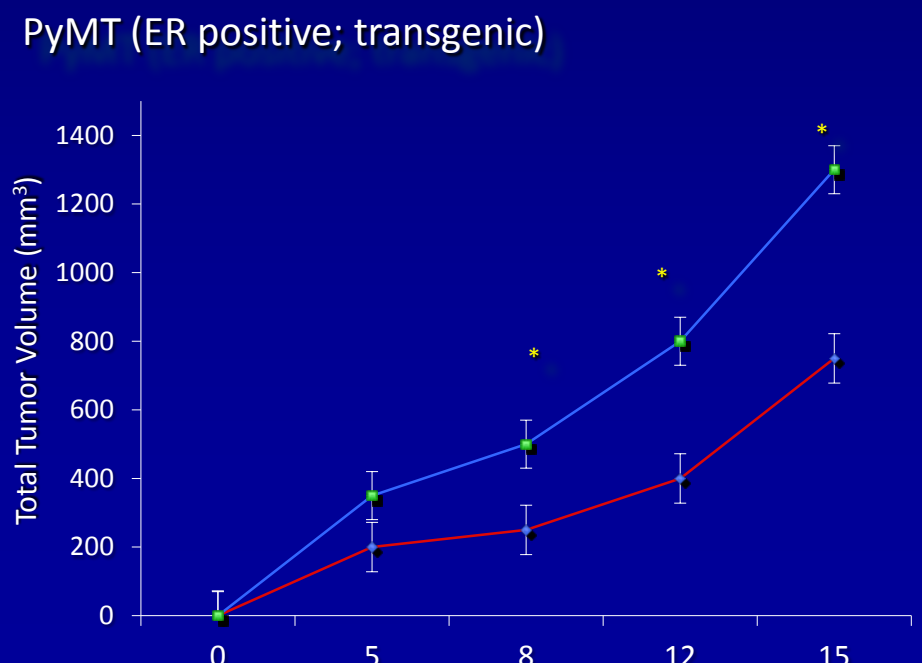
Hallmarks of cancer progression and metastatic dissemination / therapeutic outcome

Jones, AICR, 2011

Preliminary data (breast cancer)







↓ 30% - 50% tumor growth rate

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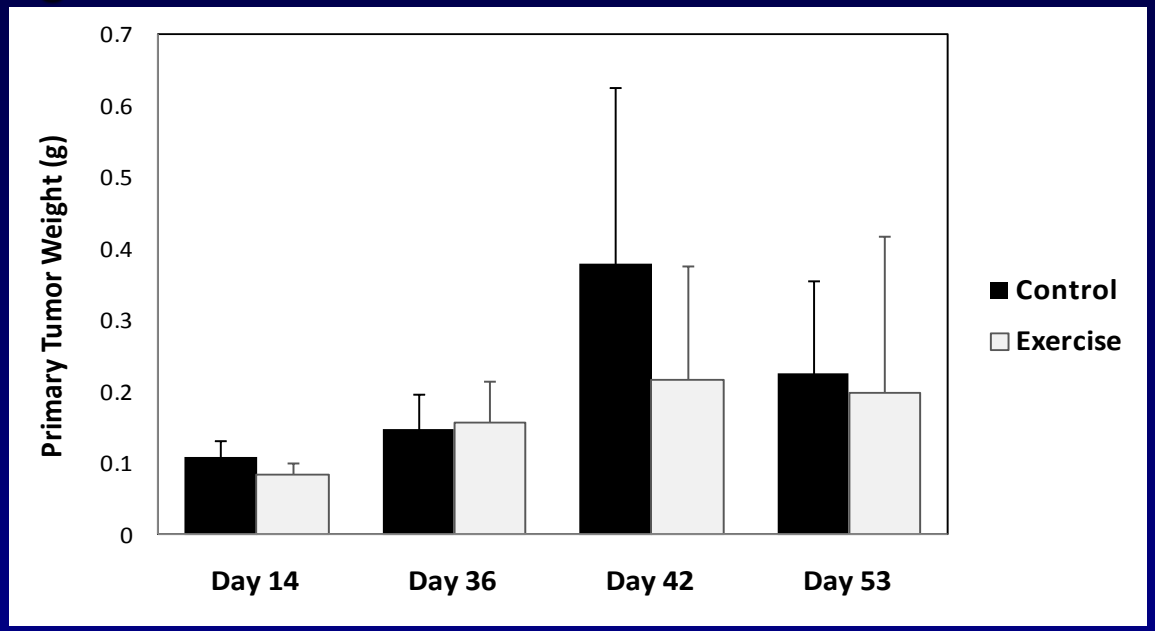
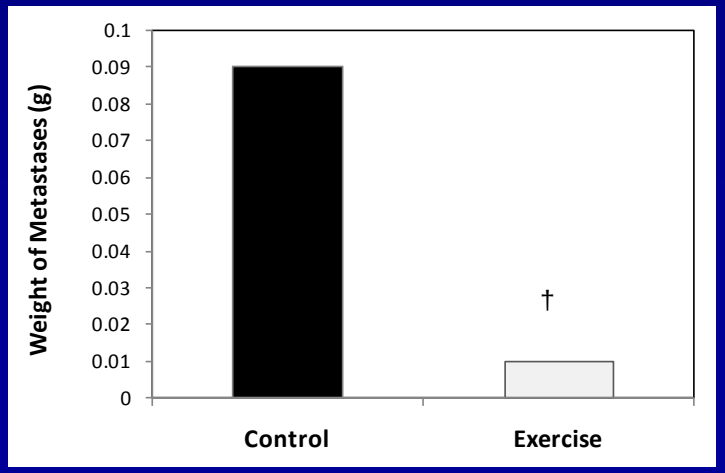
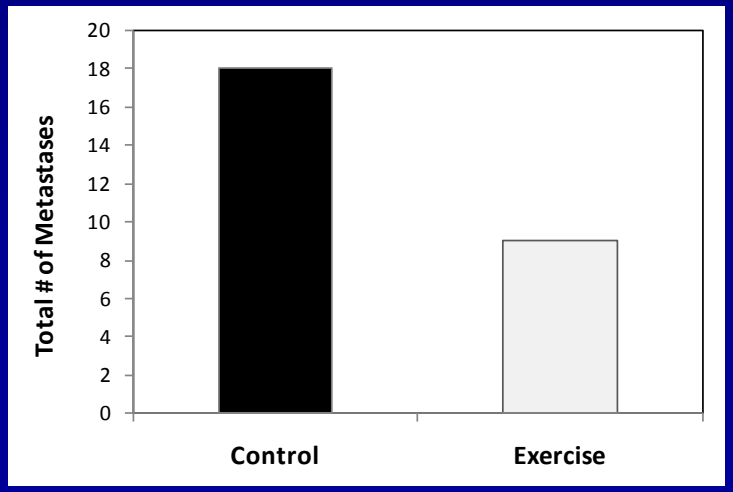
Preliminary data: prostate cancer

Primary tumor weight



Distant metastasis

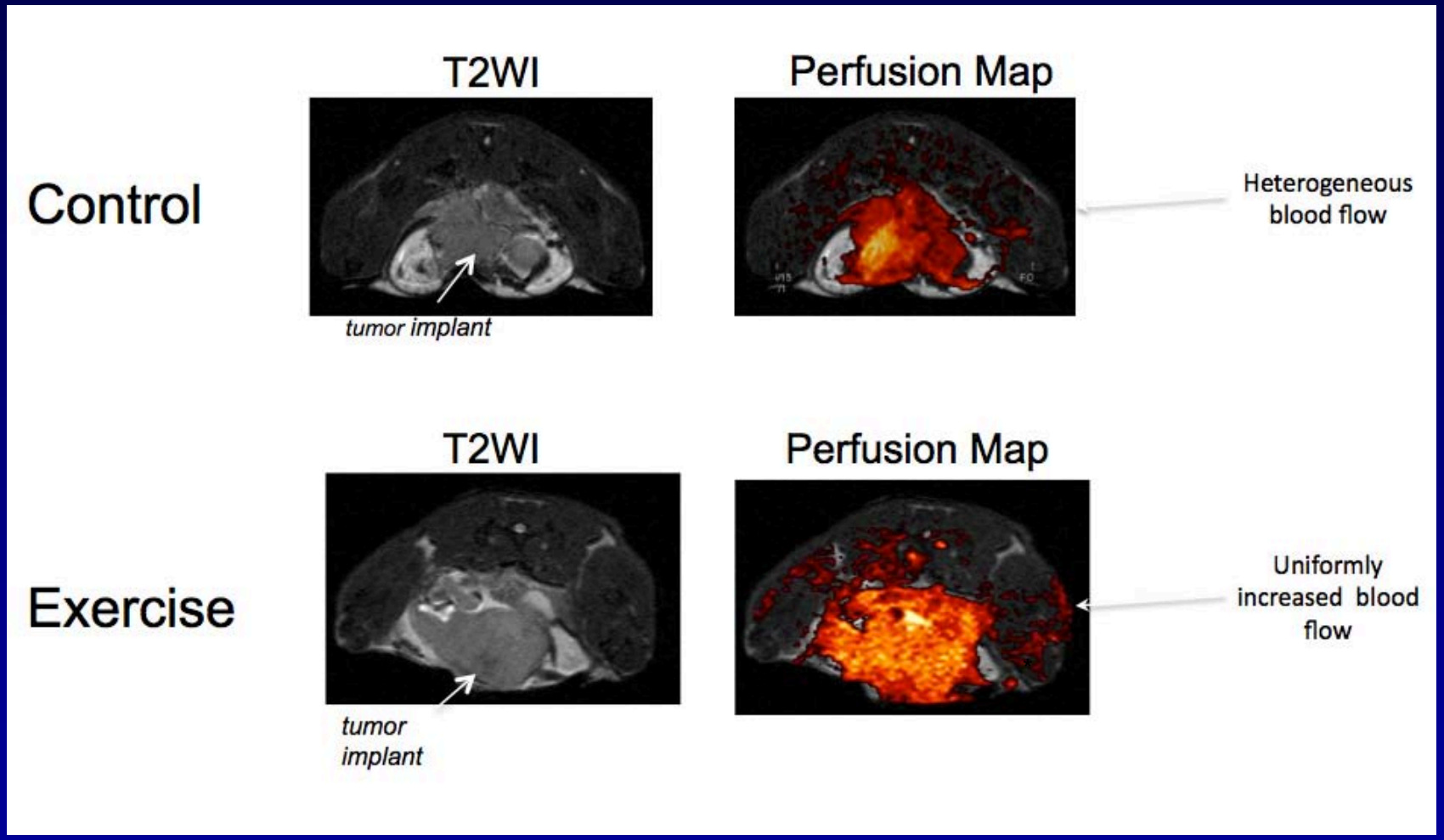




Jones et al. *Cancer Prev Res, submitted*

Jones, AICR, 2011

Preliminary data: prostate cancer



Jones et al. *Cancer Prev Res, submitted*

Jones, AICR, 2011

Preliminary data: prostate cancer

- Endurance exercise increases tumor vascularization but leads to ‘productive’ tumor angiogenesis & less aggressive phenotype
- Next steps
  - Implications to the adjuvant setting / other solid malignancies?
  - Mechanisms of action?
  - Therapeutic response / efficacy?

Jones, AICR, 2011

Aerobic training during chemotherapy

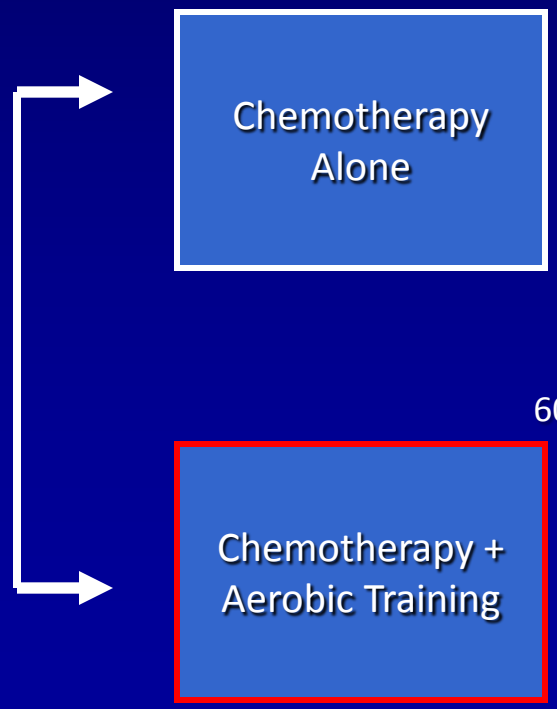
- 'Proof-of-concept' pilot study of aerobic training on plasma cytokines, bone marrow stem cells, and tumor gene expression in breast cancer pts undergoing neoadjuvant chemotherapy

Tumors >1.5 cm

LVEF >50%

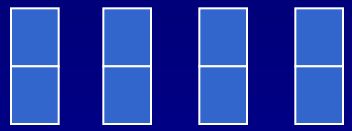
KPS >70%

n=20



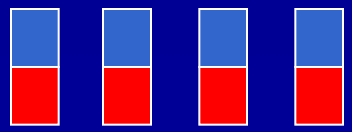
4 x AC

60/600 mg/m^2



4 x AC + ET

60/600 mg/m^2 / cycle ergomtery (3x.wk, 60% - 100% VO_{2peak} for 12 wks)



Jones et al. *in prep*

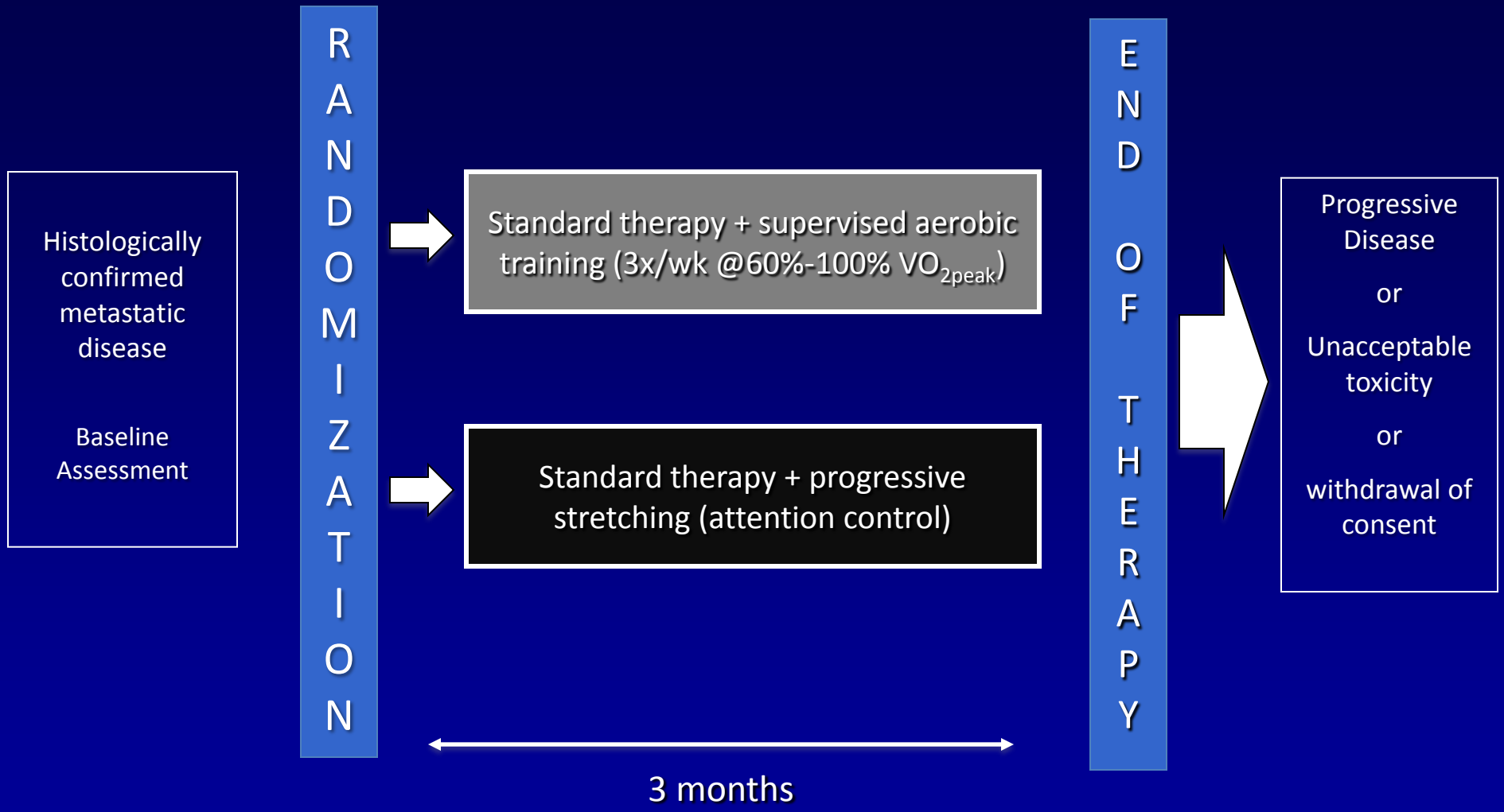
Jones, AICR, 2011

Preliminary esults

- Changes in VO_{2peak} and endothelial function (NO-bioavailability)
- Changes in circulating cytokines and angiogenic factors (e.g., IL's, PDGF)
- ↑ circulating bone marrow-derived 'stem cells' implicated in injury response / tumor angiogenesis
- Significant ↓ in tumor perfusion
- Significant changes in tumor gene expression favoring ↓ pro-migration and proliferation (less aggressive phenotype)

Jones et al. *J Natl Cancer Instit, submitted*

Metastatic feasibility trial (3-yr, R21)



- VO_{2peak}, PROs, AEs; serial bio-banking (q.3wk)
- 18 patients 'on trial'

Jones, AICR, 2011

Conclusion

- Growing research and clinical interest in exercise training (rehabilitation) following a cancer diagnosis
- Cancer not a qualifying dx for exercise rehabilitation
- Exercise training impt adjunct to prevent &/or treat cardiovascular impairment
- Exercise may be associated with prolonged survival
- Direct and correlative mechanistic data is lacking; initial results 'proof-of -concept' modulate host – tumor interaction
- Tip of the iceberg……

Jones, AICR, 2011

Acknowledgements

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