

# Case Study: Axillary Lymph Node Dissection (ALND) in Early Detected Breast Cancer

Modeling in Medical Decision Making

Chapter 5: Decision Trees

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# Breast Cancer

- 186,772 women and 1,815 men were diagnosed with breast cancer (2004)
- 40,954 women and 362 men died from breast cancer (2004)
- 12.03% of women will be diagnosed with breast cancer (based on 2003-2005)
- Median age of diagnosis is 61 (2001-2005)
- 2,477,847 women alive have been diagnosed with breast cancer
- It is the 6<sup>th</sup> leading cause of death in women (2004)

# Estrogen Receptor (ER)

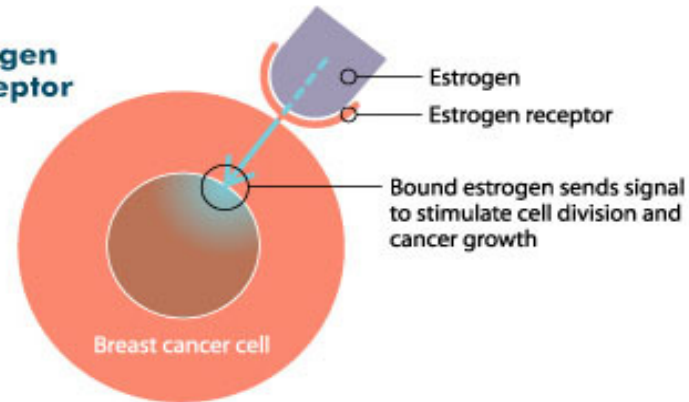
- 50-70% of breast cancer requires estrogen to grow
- The cancer cells produce estrogen receptors (ER+)
- Medication can be used to lower estrogen levels in these patients (Tamoxifen)
- Given by tablet (up to 5 years)



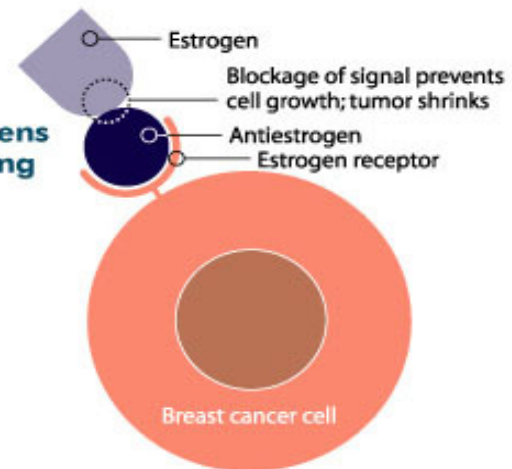
Photo source: [www.medicineworld.org](http://www.medicineworld.org)

# ER+ Medication

**Figure 1. Action of estrogen binding to estrogen receptor on cancer cell**



**Figure 2. Action of antiestrogens blocking estrogen from binding to cancer cell**



# Chemotherapy

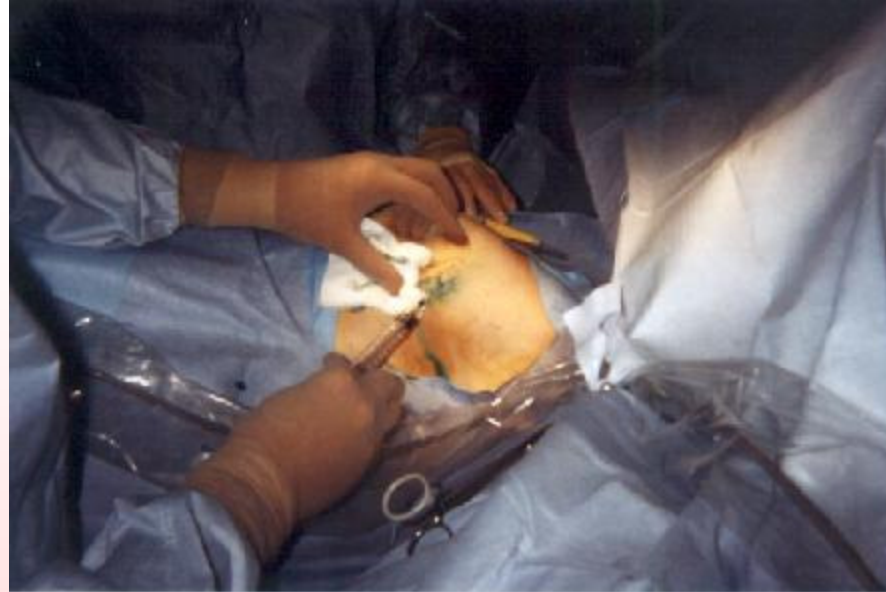
- Medication to stop or slow the growth of cancer cells
- It stops the new cells from reproducing
- This can cause side effects in other reproducing cells (ie. hair, bone marrow, and lining of the gastrointestinal tract )
- Typically given by IV



# Axillary Lymph Node Dissection (ALND)

- Minimally invasive surgery
- Radioactive dye used to find lymph nodes (began in 1991 for breast cancer)
- Remove lymph nodes near cancerous tumors
- Analyze the tumors for cancer spread

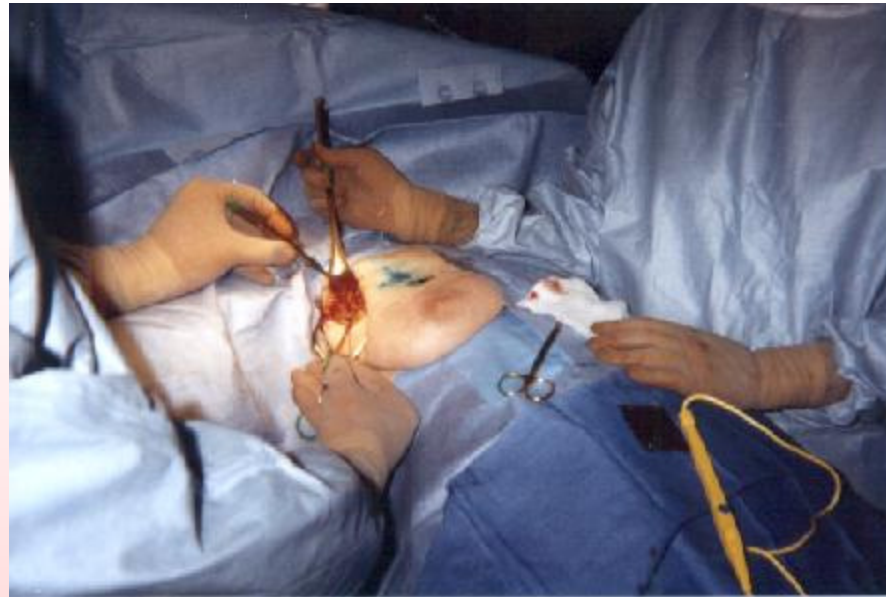
# ALND



Preparing for surgery

Injecting blue radioactive dye into the lymph system

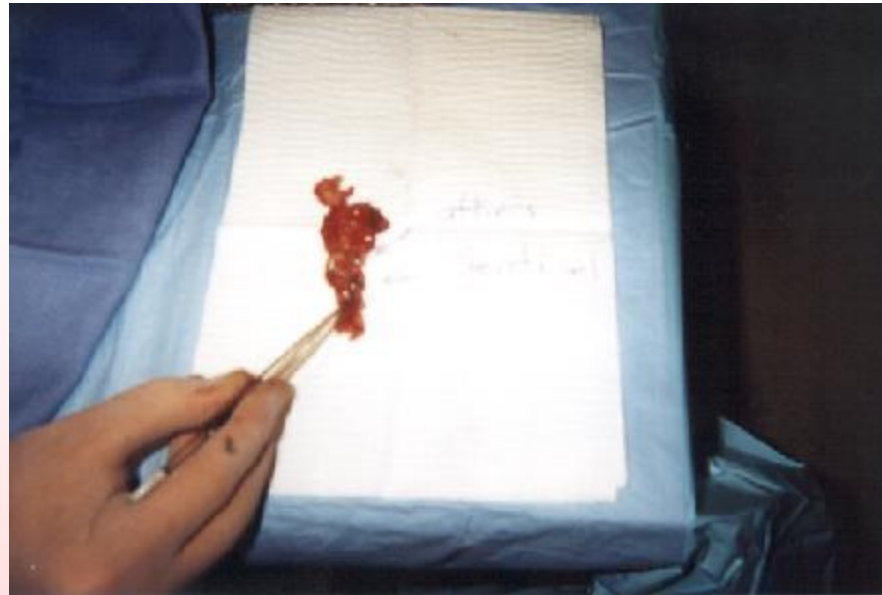
# ALND



Removing the blue stained lymph node



# ALND



Typical specimen sent to the lab for analysis

# Axillary Irradiation (XRT)

- Type of radiation treatment
- May give comparable benefits compared to ALND full removal of the node
- Does not have all of the side effects of ALND surgery ie. decreased range of motion in the shoulder, numbness, arm edema...

# Simple Decision Case

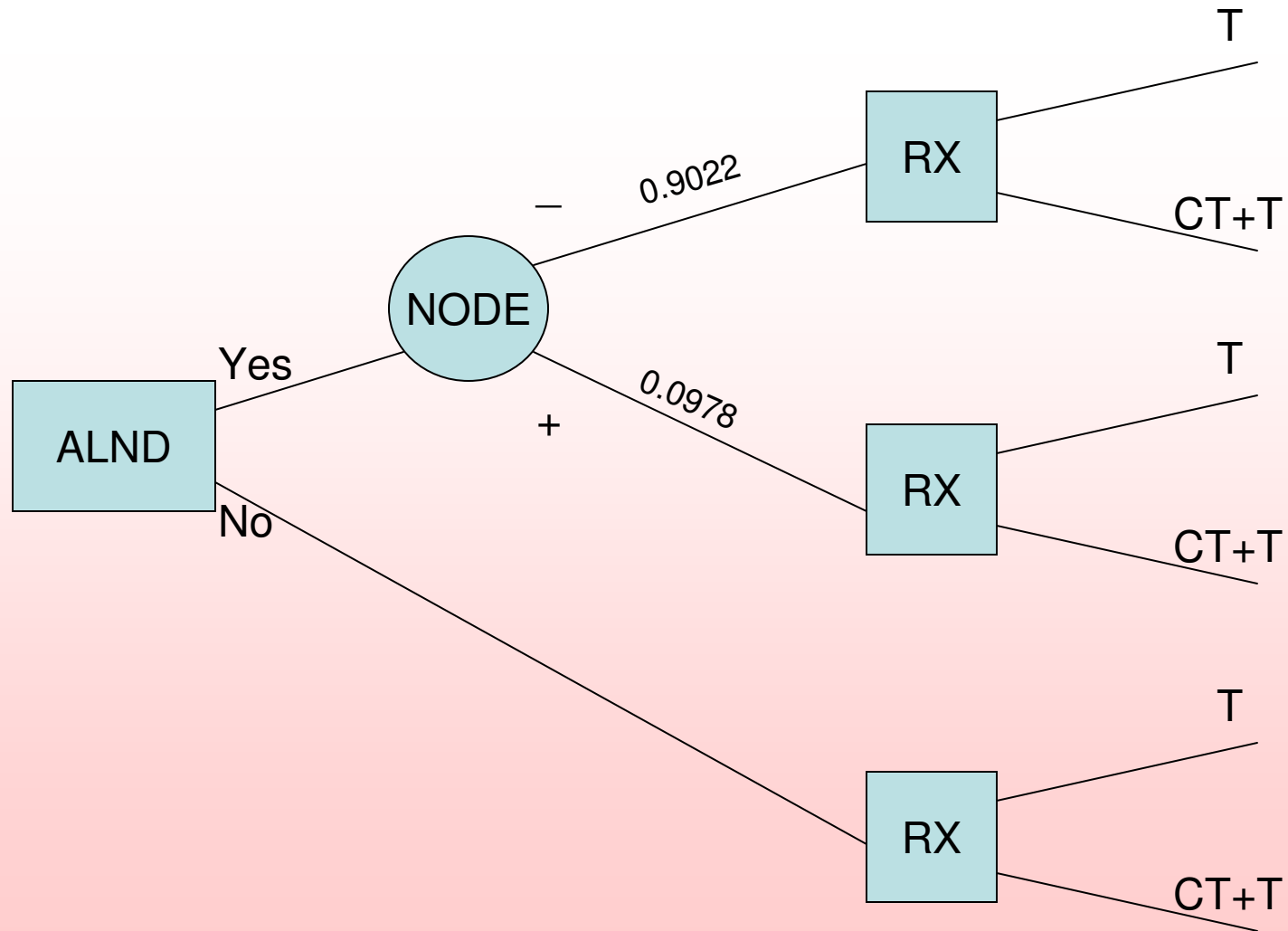
Decisions:

- ALND (surgery) vs XRT (radiation) of the lymph nodes
- Tamoxifen (T) vs Chemo+Tamoxifen (CT+T)

Cohort (study group):

- Age, ER status (estrogen tumor), tumor size
- 60 years old, ER+, tumor > 0.75 cm

# Decision Tree



# Expected QALYs

- Quality-adjusted life years (QALYs)
- A measure of quality and quantity of life lived after the treatment

QALY = length of life + side effects (QOL)

# QALY

XRT and ALND may have arm swelling, chest wall pain, mobility issues, pain...

-No treatment – adjustment =1 for QOL  
(regular life, normal diseases)

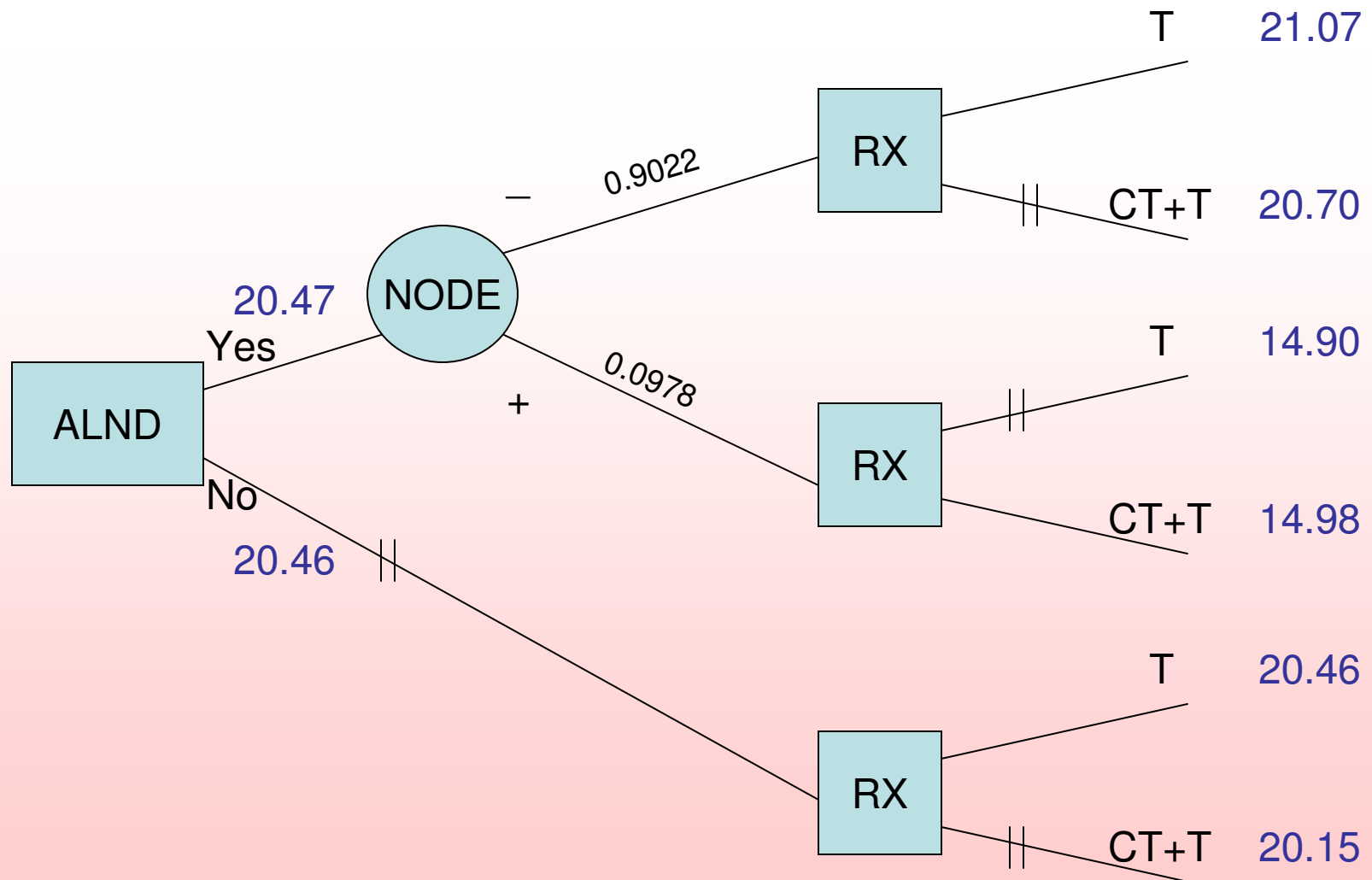
-XRT – adjustment = .997

-ALND – adjustment = .995

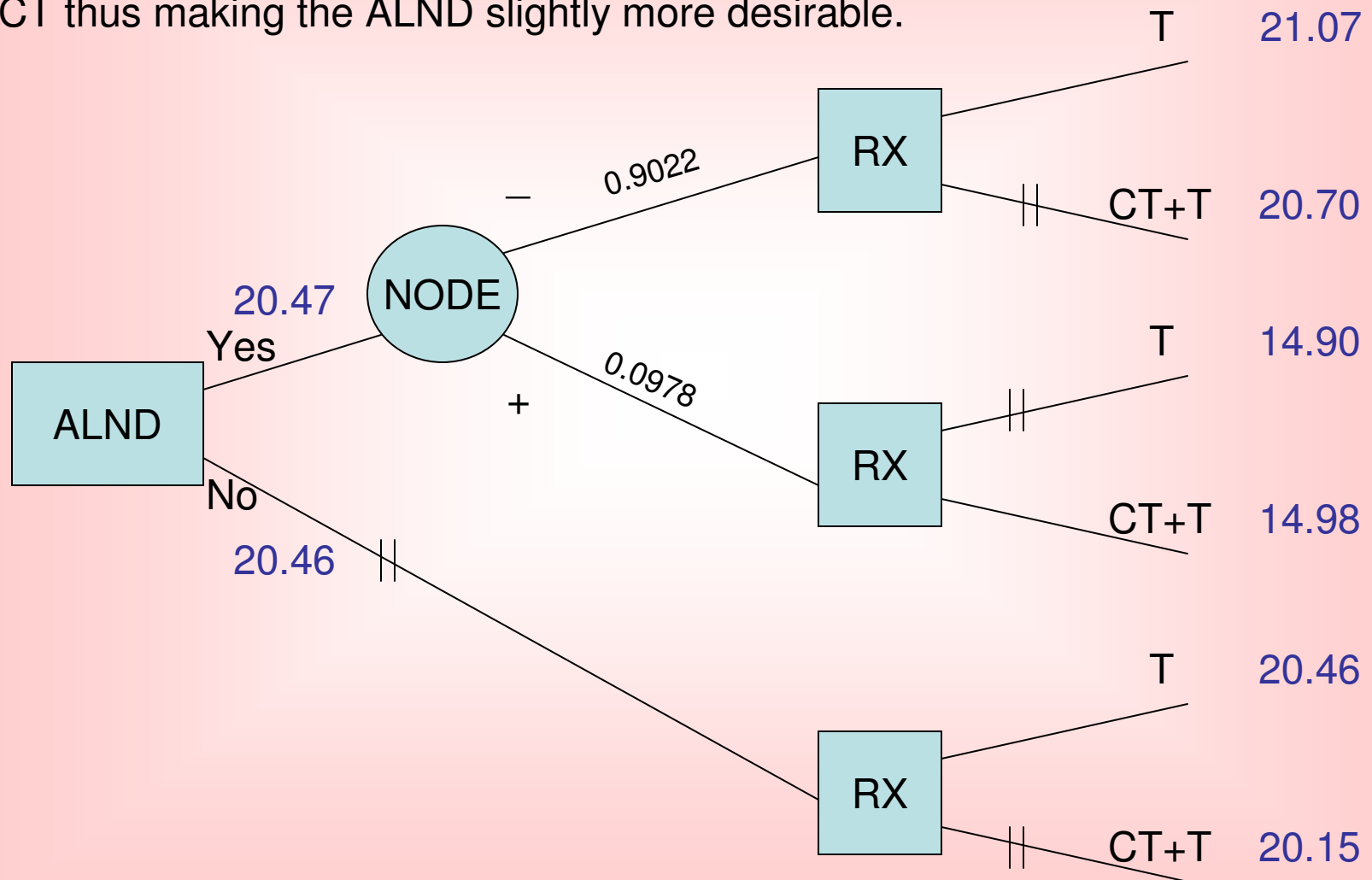
We get our QALY from  $S(t)$  the survivor function for all causes of death combined. And  $Q(t)$  is the QOL adjusted for time

$$QALY = \int_0^{\infty} S(t)Q(t)dt$$

# Backward Induction



Analysis: Do the ALND because the treatments are different for node negative and node positive patients. Chemotherapy (CT) is helpful for node positive patients, whereas it will not be used in patients opting out of ALND. 9.78% of women with node+ status get an increased benefit from CT thus making the ALND slightly more desirable.





# Bayes Action

- Cost of doing an experiment to gain information
- 2 decisions – do an experiment? which action to take?
- Before observing  $x$  we only have a prior  $\pi(\theta)$  to base our decision upon
- After observing  $x$  we have the posterior  $p(\theta|x)$  to base our decision upon

# More Theory

- Find Bayes action  $a^*(x)$  and the expected utility  $U_p(a^*(x))$  for all outcomes
- No experiment branch – decision is made based on the outcome with the highest expected utility

$$V(p) = \sup_a U_p(a)$$

- Experiment branch- decision is made based on

$$\int_X \sup_a U_p(a) dx$$

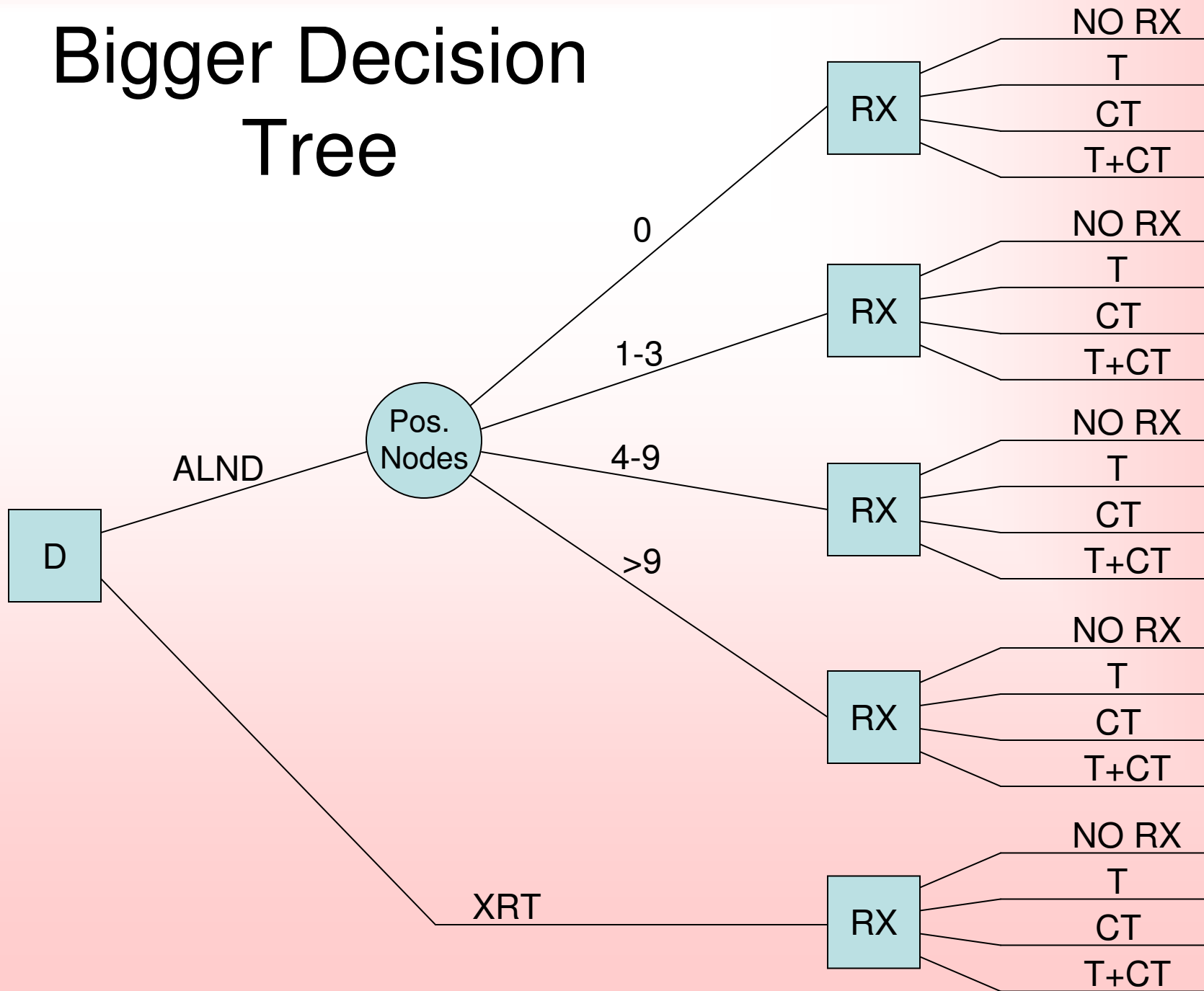
- The gain of doing the experiment is, where  $c$  is the cost:

$$\int_X \sup_a U_p(a) dx - V(p) > c$$

# Another Example

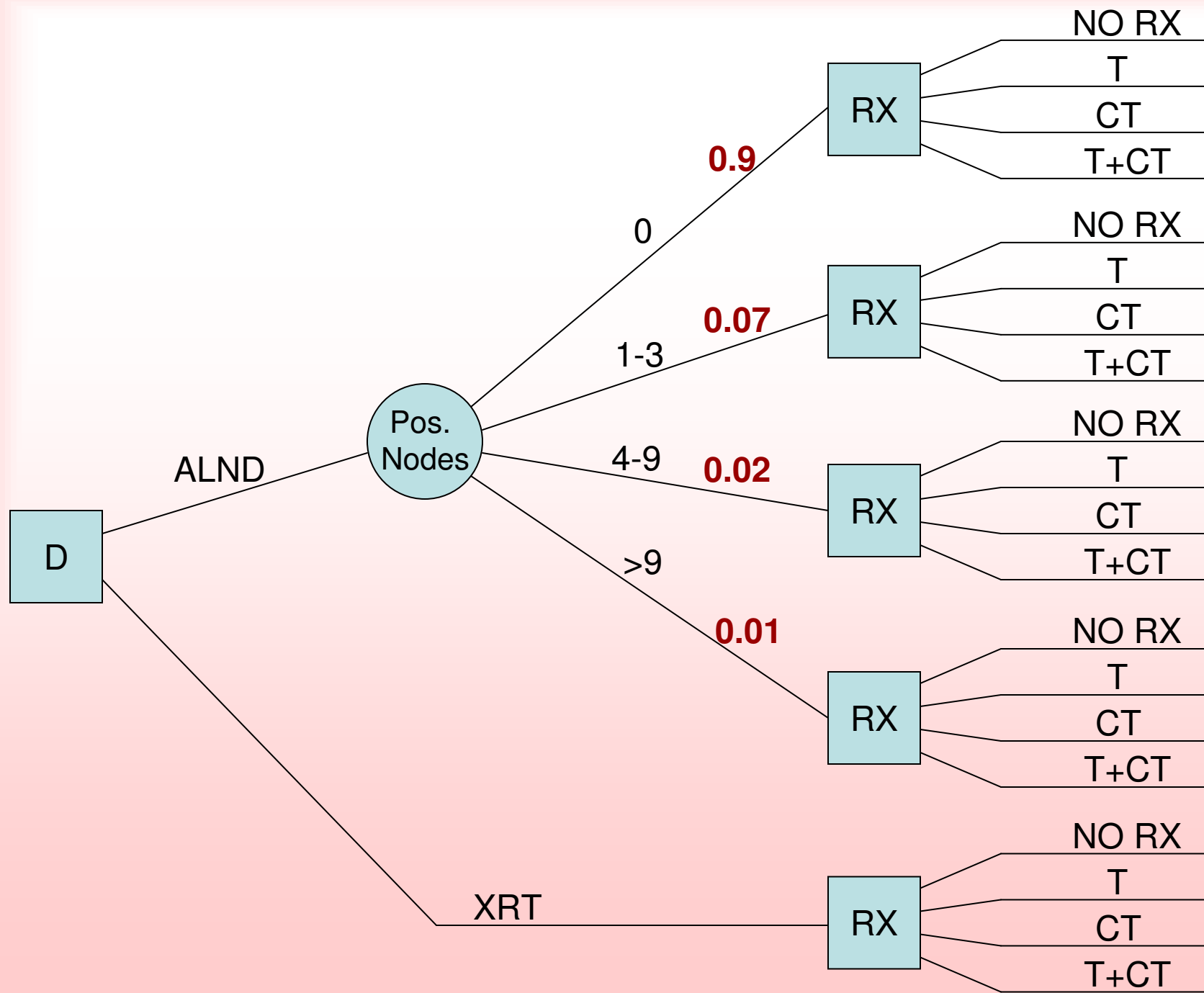
- Compare ALND to XRT
- Use a larger tree with more complexity
- Use SEER cancer registries to get probabilities for the tree
- Example: 60 year old, ER+, a tumor of 0.5-1cm

# Bigger Decision Tree

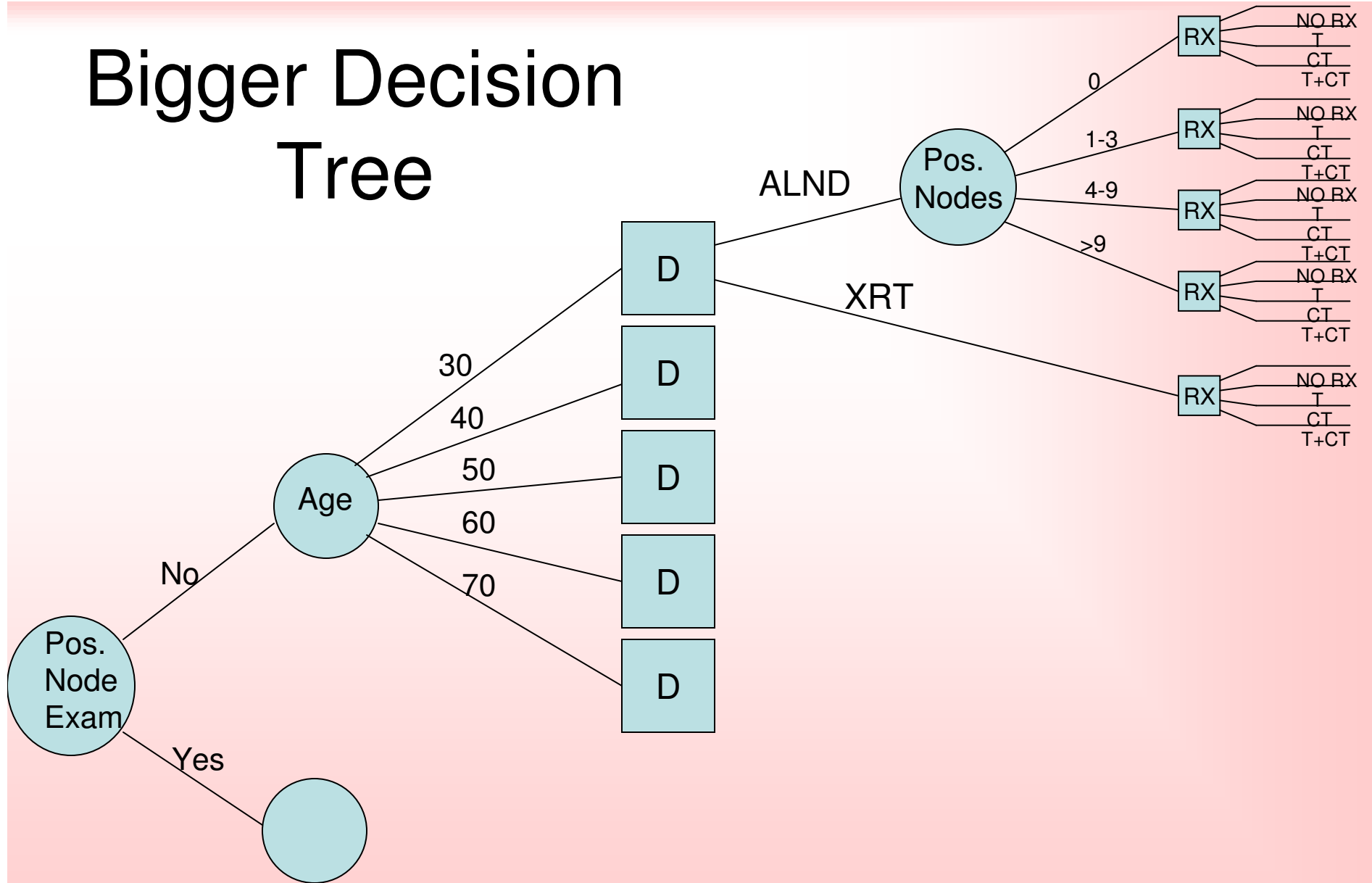


# Probabilities for the Tree

- All subjects in this tree have been screened by other means first and the nodes are not noticeably cancerous
- Adjustments to the SEERs database were made to get it to useful probabilities using Bayes' rule (SEERs includes noticeably cancerous individuals)
- 19 year follow up - beyond this the hazard rate was assumed constant to produce estimates
- Several studies were averaged together to get probabilities of node negative and node positive patients undergoing different treatments
- Life tables were used for mortality due to other effects than breast cancer
- Overall, ALND patients had a 4% (+/-4%) reduction in risk of death to XRT patients

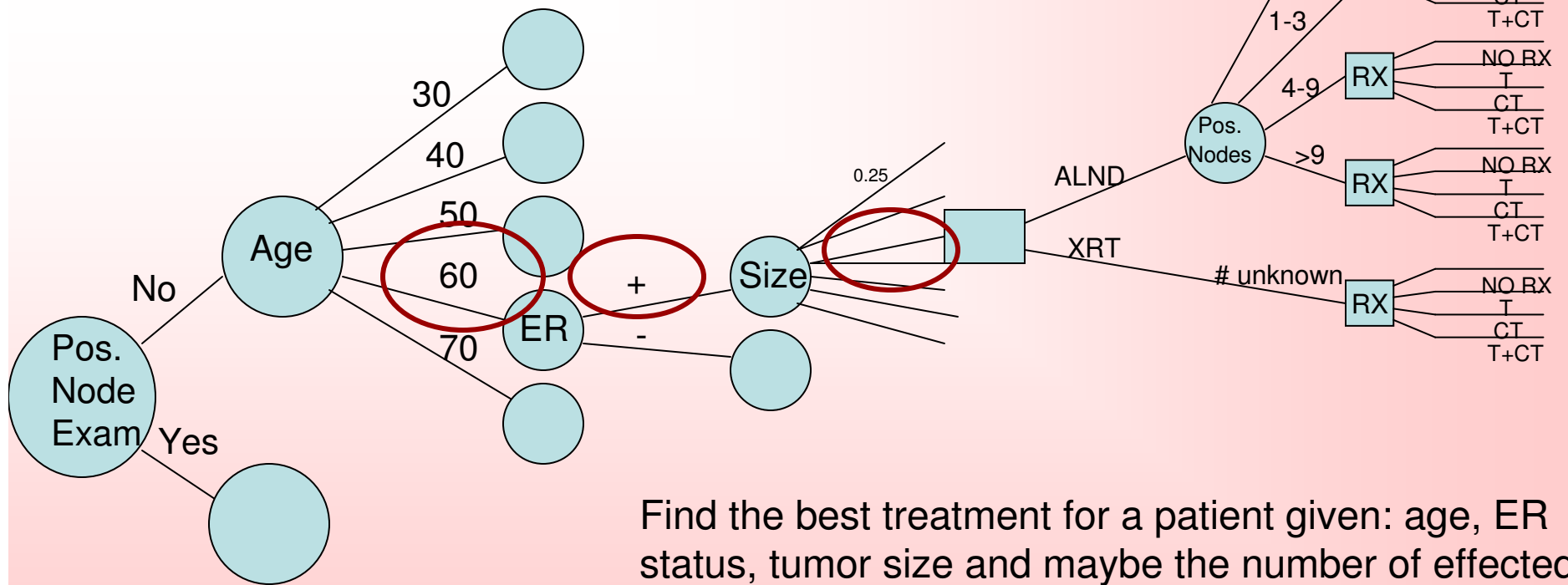


# Bigger Decision Tree



# Bigger Decision Tree

Our original small tree was a case study of just the red circled patients. The conclusion was to do the ALND and then choose CT if any nodes are positive; otherwise just use T.



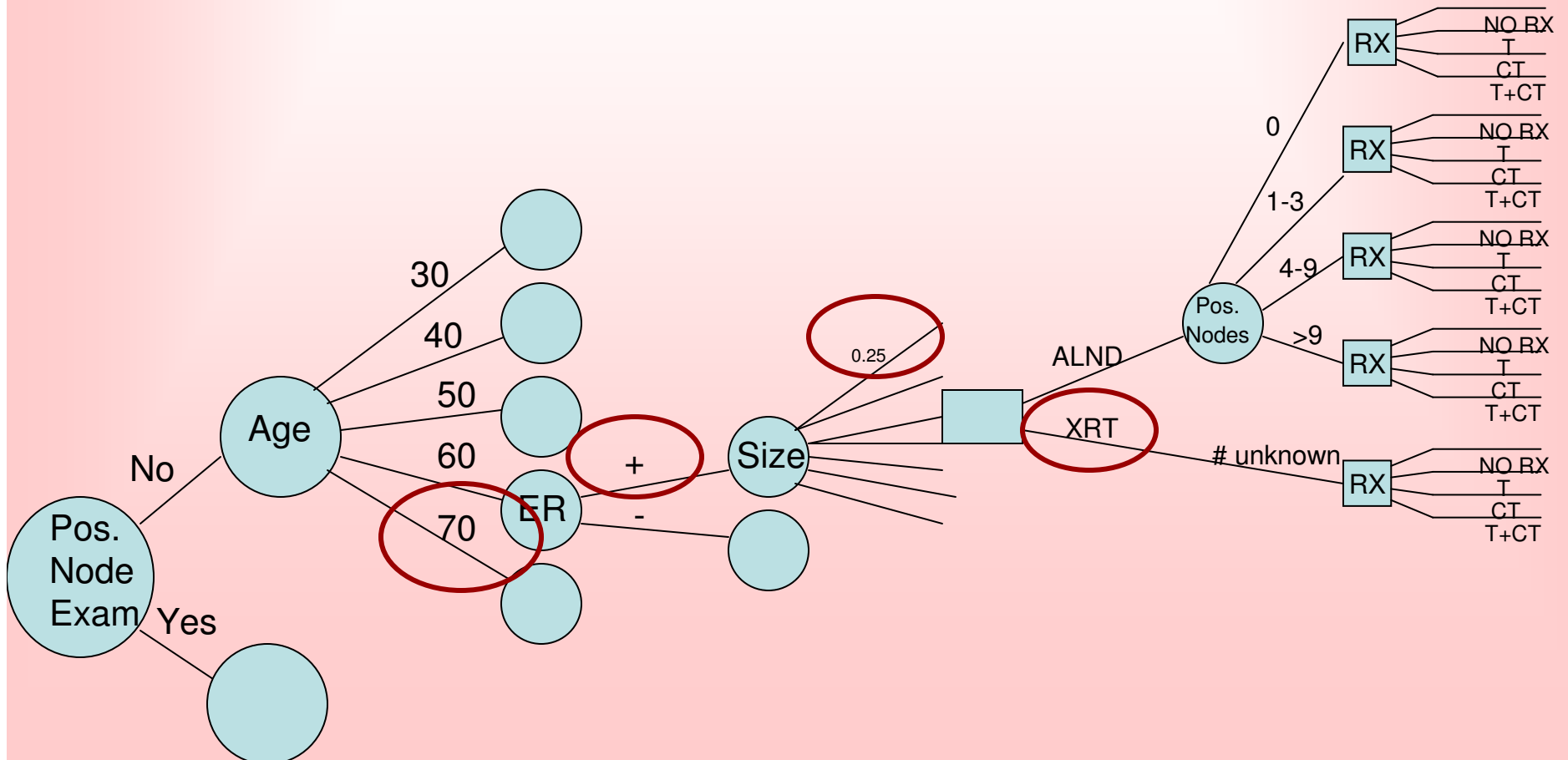
Find the best treatment for a patient given: age, ER status, tumor size and maybe the number of effected nodes.

This results in a large table of best treatments and a decision surface.



# Chart 1

There is a chart that does an overview of change in QALY for doing the ALND compared to just using XRT. The ALND provides added information which is useful in all cases except for ER+, 70 year old women with the smallest size tumors. They do not end up benefiting from the additional chemotherapy on their QALY score.



## Chart ER-

The five columns in each division are from the ALND information:  
 0 effected nodes, 1-3 effected nodes, 4-9 effected nodes, or > 9 effected nodes  
 The last column is where ALND is not preformed and therefore the number of nodes is unknown.

	30					40					50					60					70				
0.25	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	N	C	C	C	C	N	C	C	C	N
0.75	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	N	C	C	C	N
1.5	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C
2.5	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C
3.5	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C
4.5	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C
10	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C

ER- patients are not given Tamoxifen (T)

The treatment will either be Chemotherapy (C) or Nothing (N)

We see that older women with smaller tumors are the only ones that will benefit by abstaining from chemotherapy

## Chart ER+

	30	40	50	60	70
0.25	B B B B B	T B B B B	T B B B T	T B B B T	T T T B T
0.75	B B B B B	B B B B B	T B B B T	T B B B T	T T T B T
1.5	B B B B B	B B B B B	B B B B B	T B B B B	T T T B T
2.5	B B B B B	B B B B B	B B B B B	T B B B B	T T T B T
3.5	B B B B B	B B B B B	B B B B B	B B B B B	T T T B T
4.5	B B B B B	B B B B B	B B B B B	B B B B B	T T T B T
10	B B B B B	B B B B B	B B B B B	B B B B B	T B B B T

ER+ patients are usually given Tamoxifen (T)

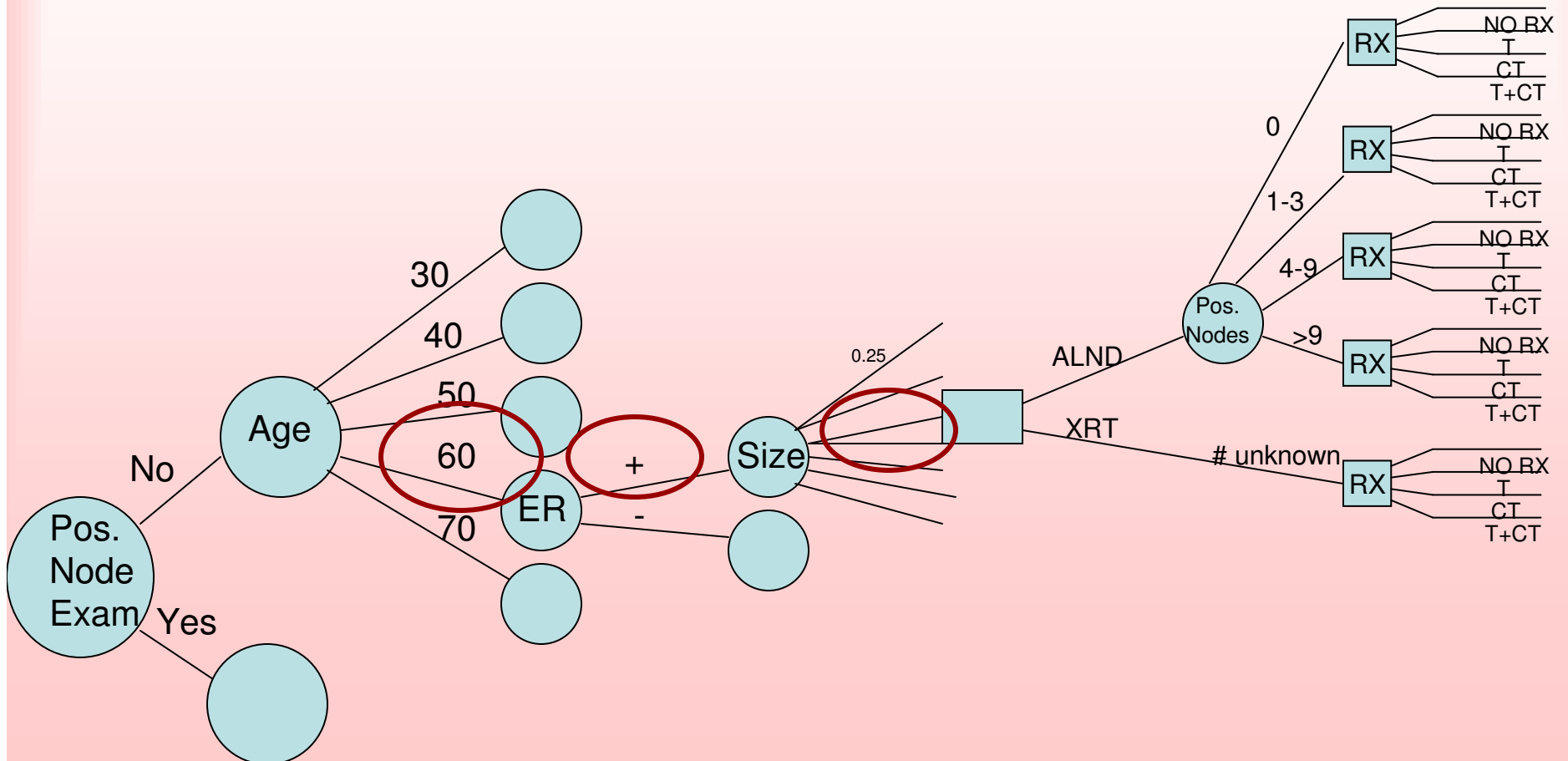
The treatment will be either Tamoxifen (T) alone or both (B) Tamoxifen and chemotherapy

-We see that older women or those with smaller tumors are the only ones that will benefit by abstaining from chemotherapy

-For 70 year old women the ALND may not change the treatment unless they have many positive nodes.

## Overall Conclusions

- Older women and ones with ER- tumors gain more information by having the ALND and may opt for the extra CT along with T if they have positive nodes.
- Younger women ALND does not provide much extra info but the effects of their decision impacts a much longer lifetime and so their QALY is highly effected.
- The QOL cost of CT is high and some may not opt for it

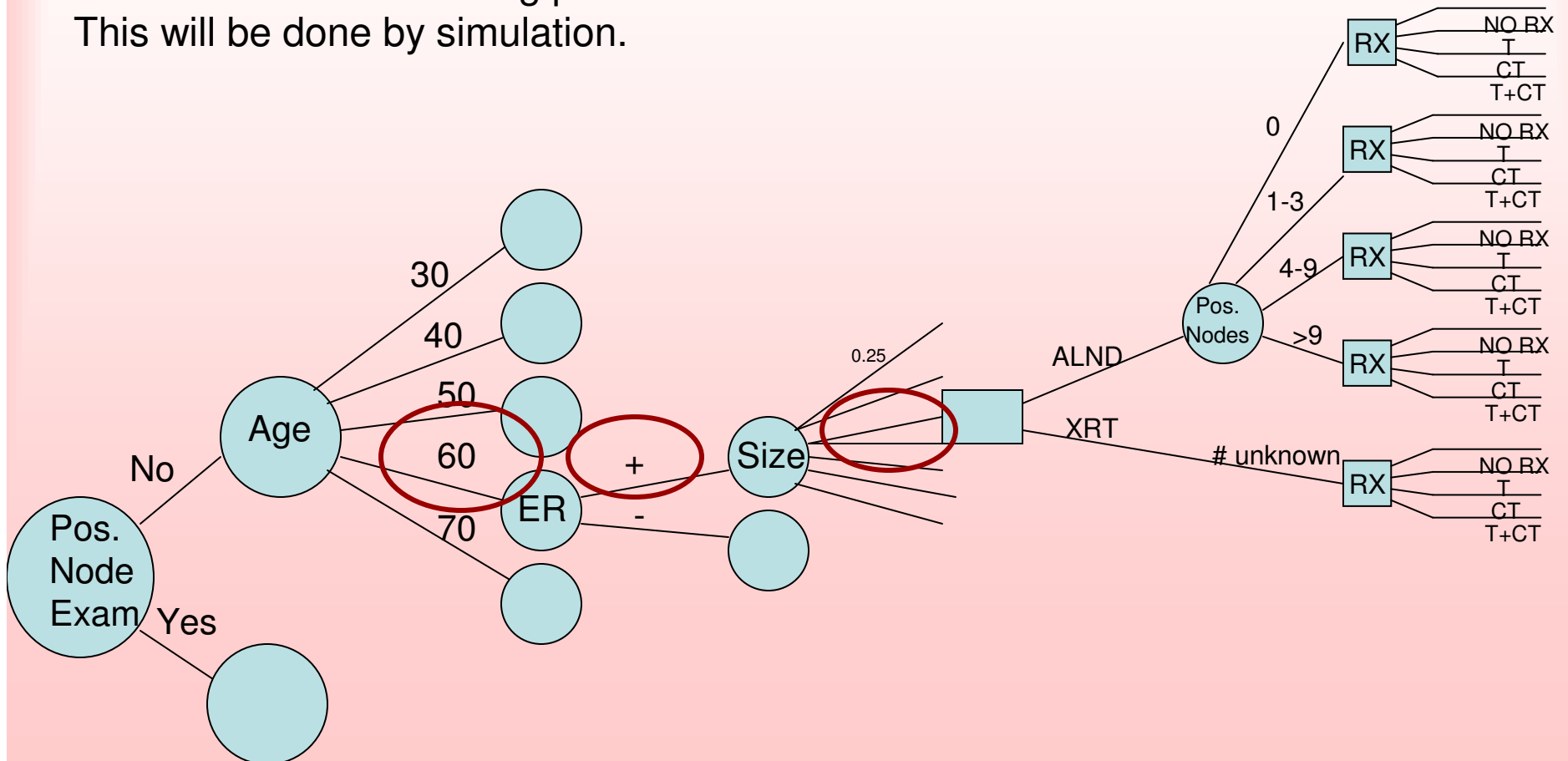


# Uncertainty

1. Uncertainty about a new woman. Will she react in a mild, moderate, or severe way to her treatment plan?
2. Uncertainty about the pool of women that made up the study; variation within the cohort making up the hazard function?

This uncertainty can be modeled in the posterior distribution for the cohort's data, so the decision making process takes this into account.

This will be done by simulation.



# Quality of Life (QOL)

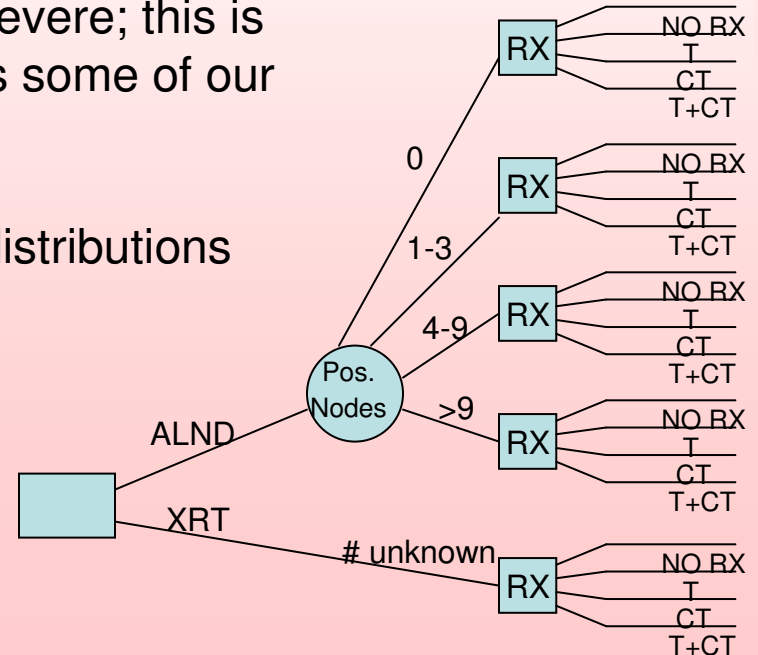
Patients were assigned to one of 3 groups depending on their quality of life (QOL)

1. Q(mild) – little impact from the treatments and completely recovers by the end of one year (82%)
2. Q(moderate) – more impact than mild
3. Q(severe)- most impact possible, like wearing a chronic compression garment or having to change jobs

# Uncertainty

Back to the simple example: 60 year old, ER+, primary tumor 0.5-1.0cm Assume uncertainty in every value and probability in this tree (all 128 parameters):

- Real valued parameters are given Normal distributions
- The probabilities of risk reduction are given Beta distributions
- SEERs data source was given Uniform priors and resulted in Dirichlet posteriors (each patient can have one of three reactions to any treatment – mild, moderate, or severe; this is not known ahead of time and will now be used as some of our uncertainty)
- The Cox hazard model coefficients were given distributions



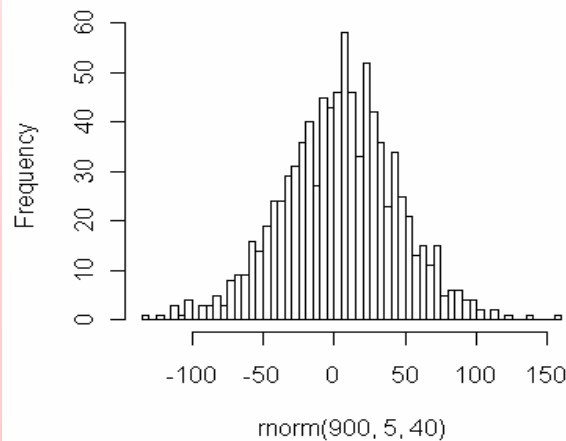
# Uncertainty

The simple example: 60 year old, ER+, primary tumor 0.5-1.0cm

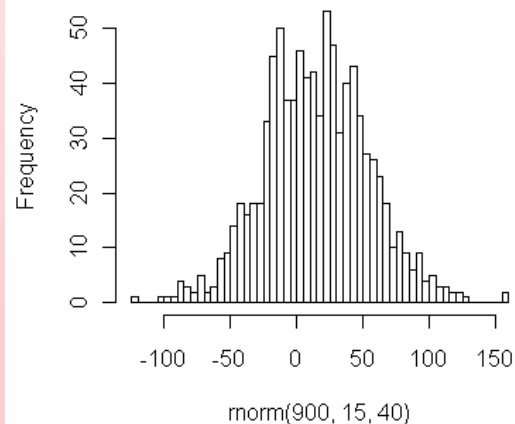
- Compare the  $\Delta$ QALY for the ALND compared to XRT
- Simulate  $\Delta$ QALY \* get an asterisk

As we can see the Mild and Moderate QOL reactions to treatment have means near zero when using the simulated outcomes; so ALND may be of little value to them. But the Severe QOL group has mostly positive values, which means most patients would benefit from the ALND and a more tailored treatment plan.

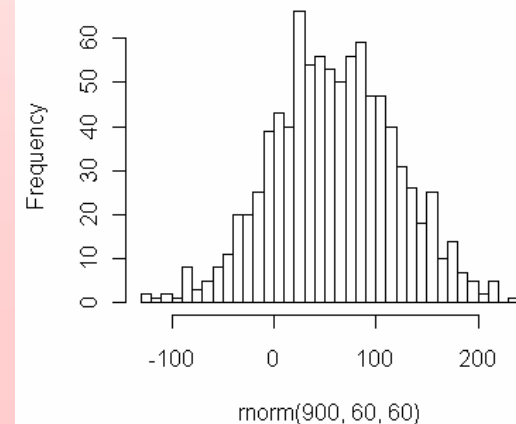
**Delta QALY- Mild**



**Delta QALY- Moderate**



**Delta QALY- Severe**





3 hypothesis of sorts given the true value of the parameters:

1. PC = the probability that the adjuvant therapy is chosen correctly – T, CT...
2. PD = the probability the ALND is of value as a diagnosis tool not as a cancer cure
3. PE= the probability that ALND is ethical- it does not inflict more harm than good

	Moderate	Severe
PC	0.29	0.03
PD	0.75	0.97
PE	0.59	0.96

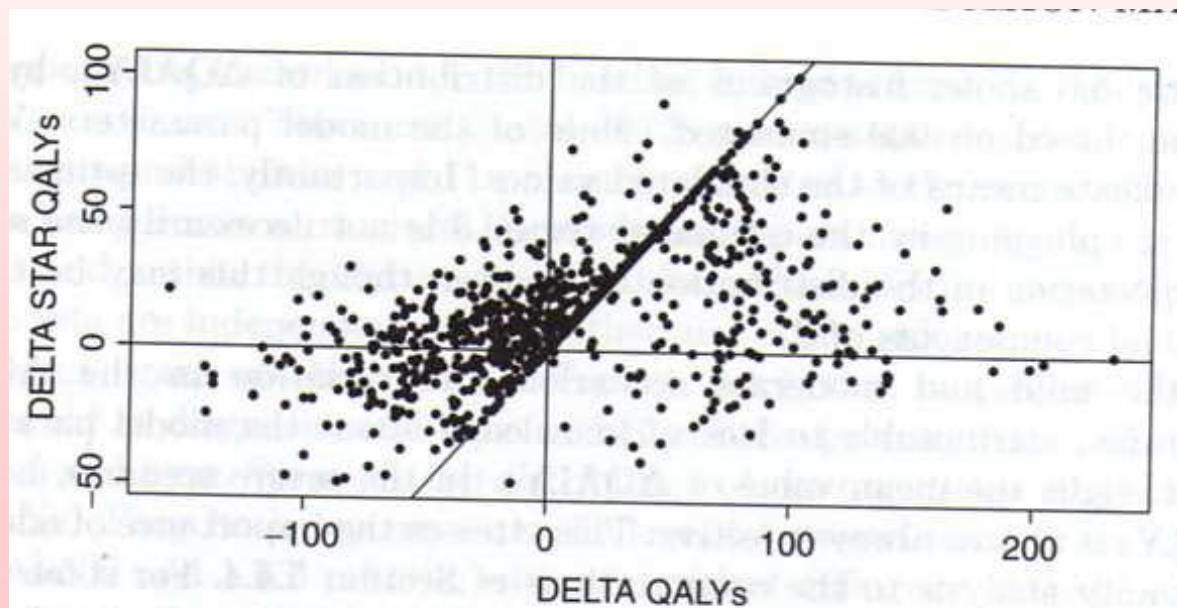
Conclusions: The severe case shows that the ALND is a helpful diagnostic tool and does not inflict unnecessary harm. The moderate case shows some favor for the ALND procedure although it is not as clear. But in both cases the second stage adjuvant decision is probably not going to be correct with this amount of uncertainty.

	Moderate	Severe
PC	0.29	0.03
PD	0.75	0.97
PE	0.59	0.96

PC = This can also be described as the event that the true value of QALY is equal to the simulated QALY\*. They are only exactly equal .29 or 0.03 in our two cases or the secondary treatment is chosen correctly (points on the x=y line)

PE =  $QALY^* > 0$  ALND is useful to make secondary decision (points above horz line)

PD =  $QALY > 0$  ALND provides more good than harm (points right of vert line)



## Other Thoughts...

-In this study, we assumed that the XRT patients should only receive Tamoxifen and not chemotherapy.

-If in ALND we find to give CT to all patients irregardless of the number of nodes effected then this would imply that all XRT patients should receive T+CT instead of the current T only treatment

There are many further directions and tests that can be performed on the tree now that uncertainty has been added



# Decision Tree

