Risk Prediction for Premature Menopause in Childhood Cancer Survivors

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Background and Objectives

Mortality in Childhood Cancer

- 5-year survival rate improved from 30% in the 1960s to above 80% today (USA, SEER data).
- Certain types such as ALL demonstrated one of the most impressive increases.
- Clinical Concerns: late treatment effects.

Late Effects in Childhood Cancer Survivors

- Serious chronic health problems in adult survivors
  - Congestive heart failure
  - Cerebrovascular accident
  - Major joint replacement
  - Hearing loss
  - Blind
  - Ovarian failure

Ovarian Failure

Acute Ovarian Failure (AOF): A loss of ovarian function during or shortly after cancer therapy, typically within 5 years of diagnosis.

Nonsurgical Premature Menopause (NSPM): Ovarian function is normal for at least 5 years after cancer diagnosis, but spontaneous amenorrhea presents for a minimum of 6 months before age 40.

Incidence Rate in Survivors and Clinical Implications

Acute Ovarian Failure: ~6.5%

Nonsurgical Premature Menopause: ~9.5%

Ovarian Failure greatly reduces a survivor's reproductive window

Clinician's challenge: limited information to counsel patients and survivors regarding their fertility preservation needs

Study Objectives

To develop a clinically useful risk prediction tool to quantify the *absolute risk* of developing ovarian failure, i.e. AOF and NSPM by specific ages.

How to use?

- Low risk patient: Reassuring patients and survivors
- High risk patient: Discussing different fertility preservation options
  - ovarian tissue cryopreservation (requires surgery)
  - oocyte cryopreservation (only available for post puberty and can be traumatic for teenage females)

Approach

Childhood Cancer Survivor Study

A retrospective cohort study of childhood cancer survivors from across North America (over 20,000 individuals diagnosed between 1970 to 1999).

Focusing on the impact of cancer treatment on the development of chronic conditions later in life.

- Baseline survey and follow-up surveys that include menstrual history

Ovarian Status Ascertainment

- AOF: Survivor is considered to have AOF if she reported never menstruating by age 18 or spontaneous amenorrhea within 5 years of cancer diagnosis.
- NSPM: Survivors without AOF are considered to have NSPM if they reported spontaneous amenorrhea before age 40.

Study Population

Female Survivors	n
Total Cohort	11,336
Available to research question	**8,770**
75% allocated for training (the rest 25% reserved as internal validation data)	6,437
Pituitary dysfunction or cranial radiation	609
Overlap with SJLIFE (external validation data)	672
Missing age at PM or age at diagnosis	54
Second malignancy within 5 years	6
Total	**5,096**
Missing CED or Missing ovarian radiation dosage (the main exposure variables)	792
Complete Data	**4,304**

Treatment Exposures

		Treatment Period					
		1970-74	**1975-79**	**1980-84**	**1985-89**	**1990-94**	**1995-99**
CED (g/m^2)	% Yes (CI)	31.7% (27.2%, 36.5%)	39.3% (35.7%, 43%)	50.8% (47.6%, 54%)	49.5% (46.3%, 52.7%)	52.2% (49.1%, 55.3%)	54.8% (51.6%, 58%)
	Median (IQR)*	11.0 (6, 17.5)	9.7 (5.5, 14.3)	5.8 (2.9, 11.2)	6.1 (2.8, 10.39)	5.7 (2.0, 11.0)	4.8 (2.1,10.1)
Minimum Ovarian RT Dose (Gy)	% Yes (CI)	69.8% (65.1%, 74.2%)	67.7% (64.1%, 71.1%)	53.1% (49.9%, 56.4%)	33.9% (30.8%, 36.9%)	24.5% (21.9%, 27.2%)	26.5% (23.7%, 29.4%)
	Median (IQR)*	9.2 (1.2, 5.4)	1.2 (0.4, 11.0)	1.1 (0.3, 9.0)	0.8 (0.2, 7.2)	0.8 (0.2, 7.1)	0.6 (0.3, 11)

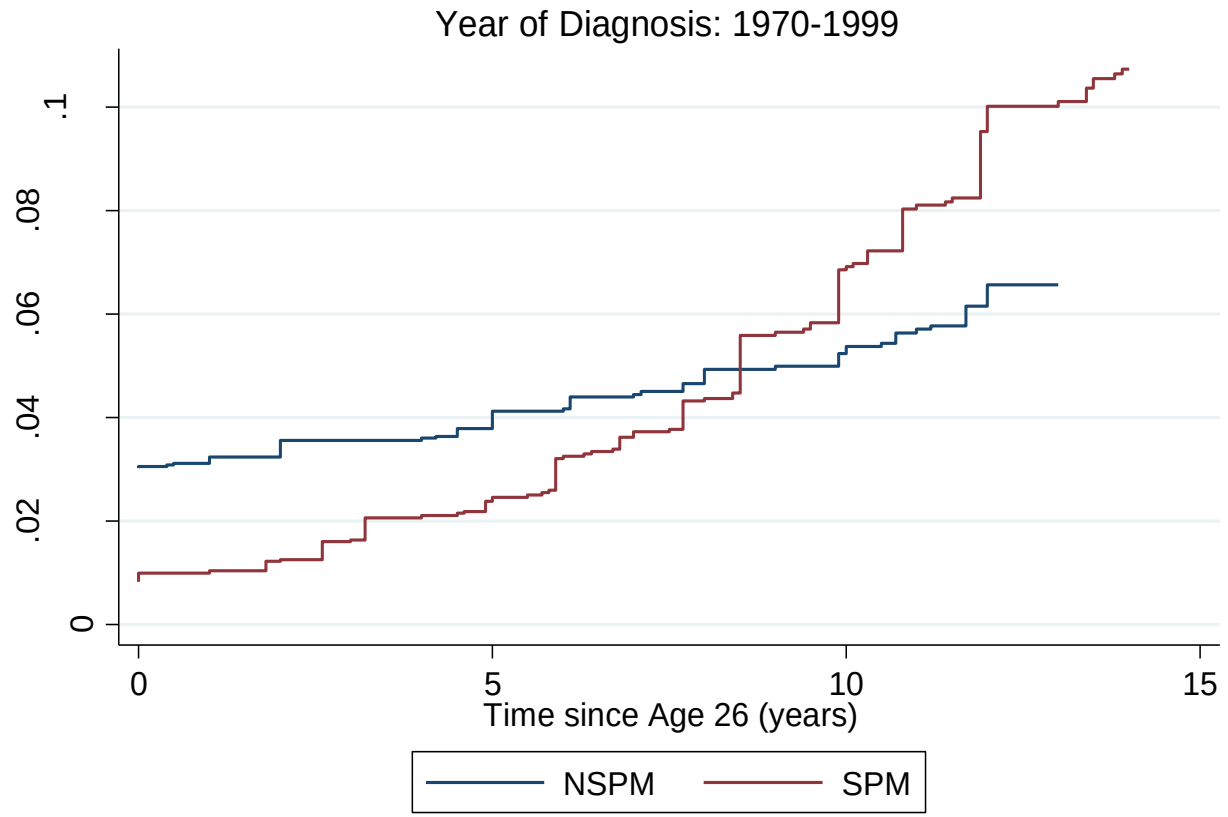
AOF Prevalence

	Treatment Period					
	1970-74	**1975-79**	**1980-84**	**1985-89**	**1990-94**	**1995-99**
AOF	10.1% (7.3%-13%)	6.1% (4.5%-8.2%)	3.4% (2.3%-4.8%)	3.1% (2.0%-4.2%)	5.2% (3.8%-6.6%)	8.2%* (6.5%-10%)
5-year Survival Rate (SEERs)	-	62.8%	67.8%	72.9%	76.8%	79.5%

Overall rate: 5.9%

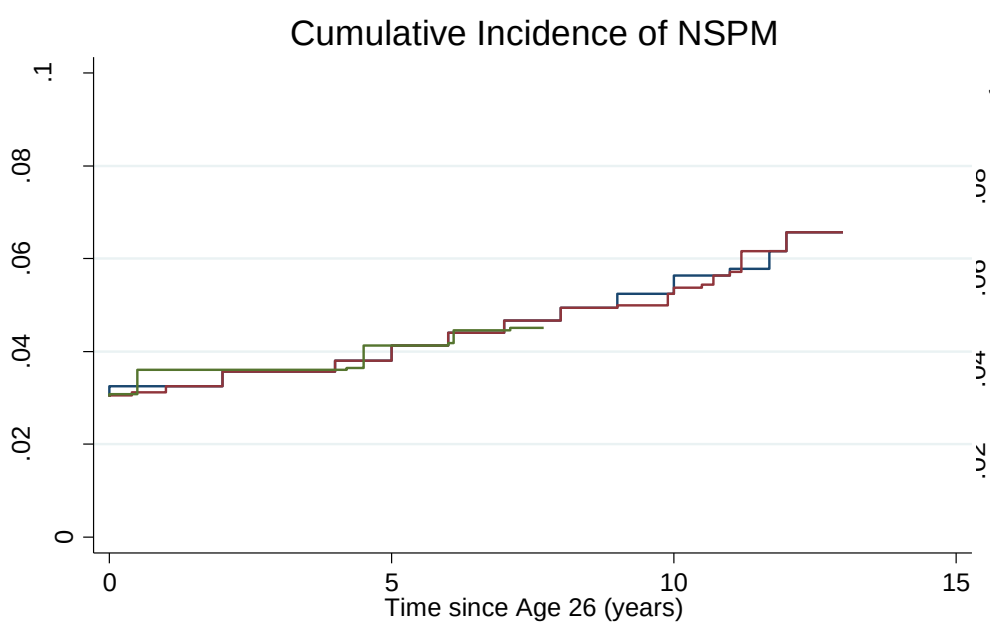
*A proportion has not reached age 18 in this diagnosis period at last survey and thus were not included in the analysis.

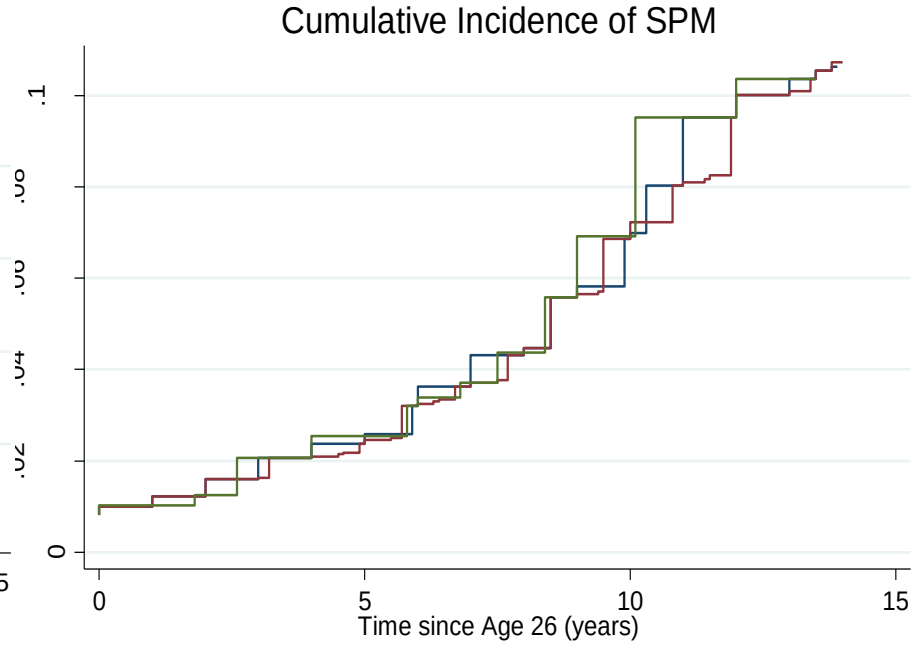
Cumulative Incidence Curves

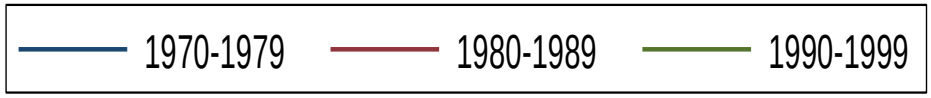


NSPM Baseline Prevalence (at 26 years old): 3.02%
SPM Baseline Prevalence (at 26 years old): 0.81%

Cumulative Incidence Curves







Challenges in Modelling

- Surgical Premature Menopause (SPM)
  - Within five-year of cancer diagnosis (competing with AOF)
  - During survivorship (competing with NSPM)

How to treat the subjects with SPM in the risk prediction model for NSPM?

Modelling AOF

- Logistic Regression

$$\text{logit}(\Pr(\text{AOF}|X_i)) \equiv \log \frac{\Pr(\text{AOF}|X_i)}{1-\Pr(\text{AOF}|X_i)} = \beta_0 + \sum \beta_k X_k$$

Modelling NSPM

1. Cox Proportional Hazards Model

$$\lambda_i(t) = \lambda_0(t)\exp(\Sigma\beta_k X_{ki})$$

2. Time-Specific Logistic Regression

$$\text{logit}(\Pr(\text{NSPM} \mid X_i)) = \beta_0 + \Sigma\beta_k X_{ki}$$

Variables Assessed for Inclusion

Chemotherapy

- CED and Procarbazine Dose
- Chemotherapy associated with stem cell transplant (yes/no)

Radiation

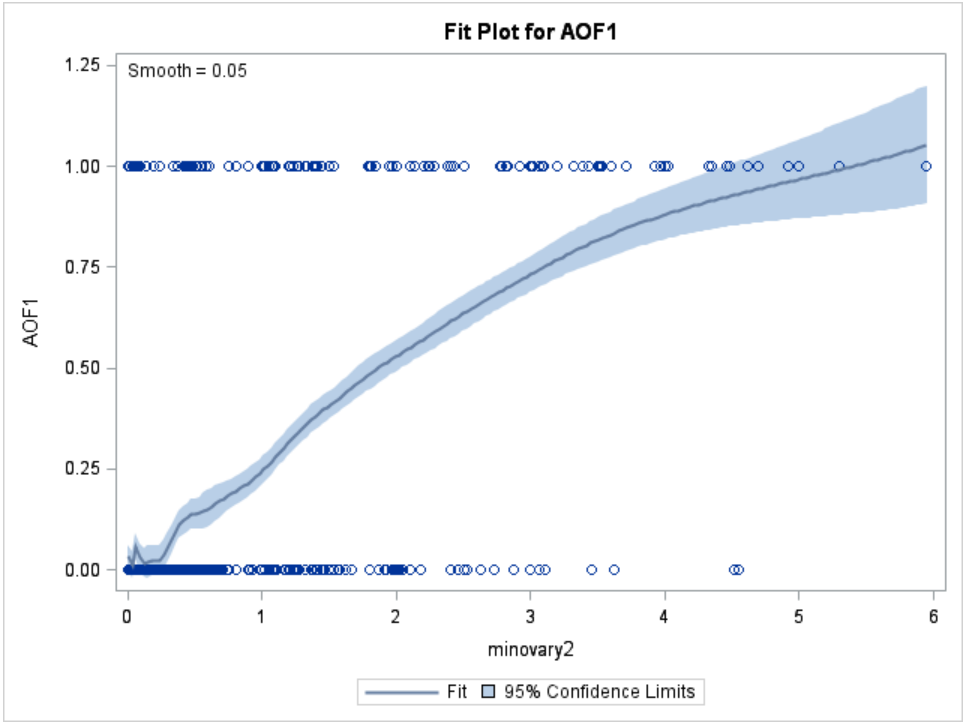
- Minimum Ovarian Radiation Dose
- TBI Exposure (yes/no)

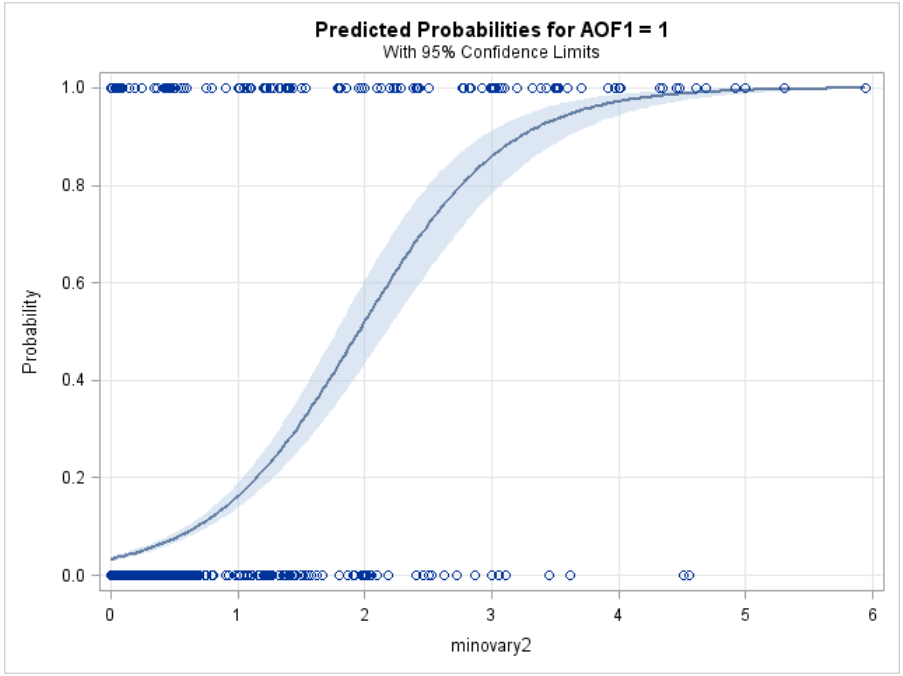
Others

- Age at Diagnosis
- Age at Menarche
- Treatment Era

Results

Ovarian Radiation Dose and AOF





Cox PH Models

Predictors	Hazards Ratio	p-value
Age at Diagnosis	1.03	0.041
Chemotherapy (g/m^2)		
CED minus Procarbazine	1.01	0.4
Procarbazine Dose	1.23	<0.001
Radiation		
TBI Exposure (Yes vs. no)	2.35	0.078
Minimum Ovarian Dose (Gy)	1.08	<0.001
Treatment Period		
1975-1979	0.71	0.271
1980-1984	0.66	0.169
1985-1989	1.3	0.388
1990-1994	1.59	0.119
1995-1999	1.59	0.178

TLR Models: at Age 30

Predictors	Odds Ratio	p-value
Age at Diagnosis	0.81	<0.001
Chemotherapy (g/m²)		
CED minus Procarbazine	1.003	0.836
Procarbazine Dose	1.002	0.983
Radiation		
TBI Exposure (Yes vs. No)	2.02	0.418
Minimum Ovarian Dose (Gy)	1.10	<0.001
Treatment Period		
1975-1979	0.51	0.23
1980-1984	0.85	0.726
1985-1989	3.39	0.008
1990-1994	19.99	<0.001
1995-1999	37.71	<0.001

Prediction Performance

Discrimination

The ability of the diagnostic test to correctly classify the outcome as positive (event observed) or negative (no event observed)[3]

Area under the ROC Curve (**AUC_t**)

- Gives the probability that a randomly chosen observation with a positive outcome will be ranked higher than a randomly chosen observation with a negative outcome[4]
- Range: from 0.5 to 1
- 0.6 fair 0.7 good 0.8 ~ 0.9 excellent

Prediction Accuracy

Average Positive Predictive Value (**AP_t**)

- Value of the area under the precision-recall (PR) curve
- Range: from the population prevalence rate of event to 1

Calibration

Concept: The estimated probability is “trustworthy”.

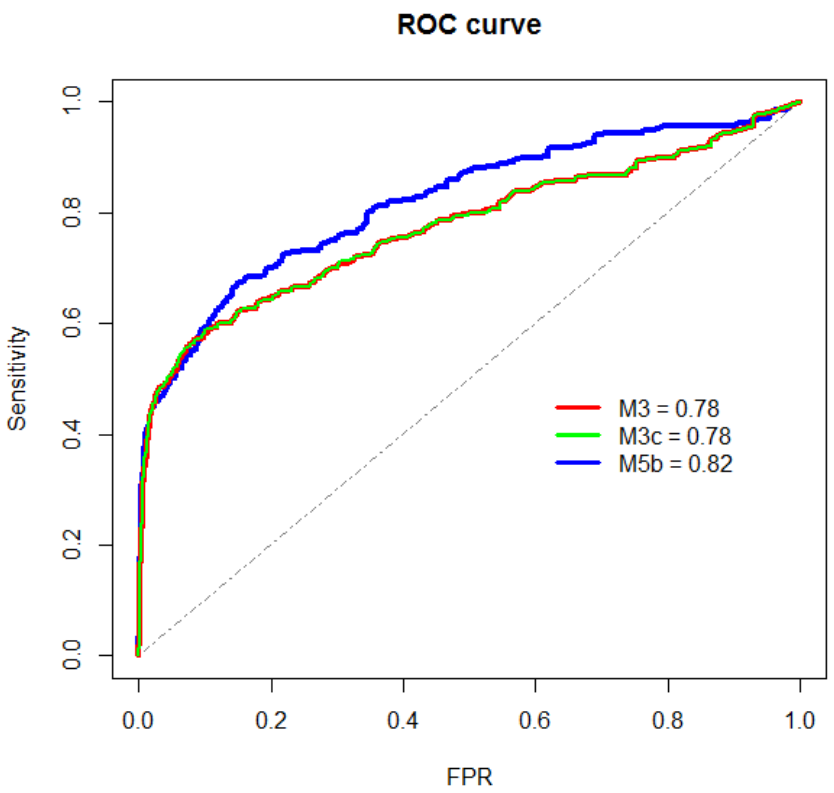
Calibration plot:

Group subjects with similar estimated probabilities together and examine the actual number of “cases” in the group with the estimated number of cases (by summing the estimated probabilities in the group).

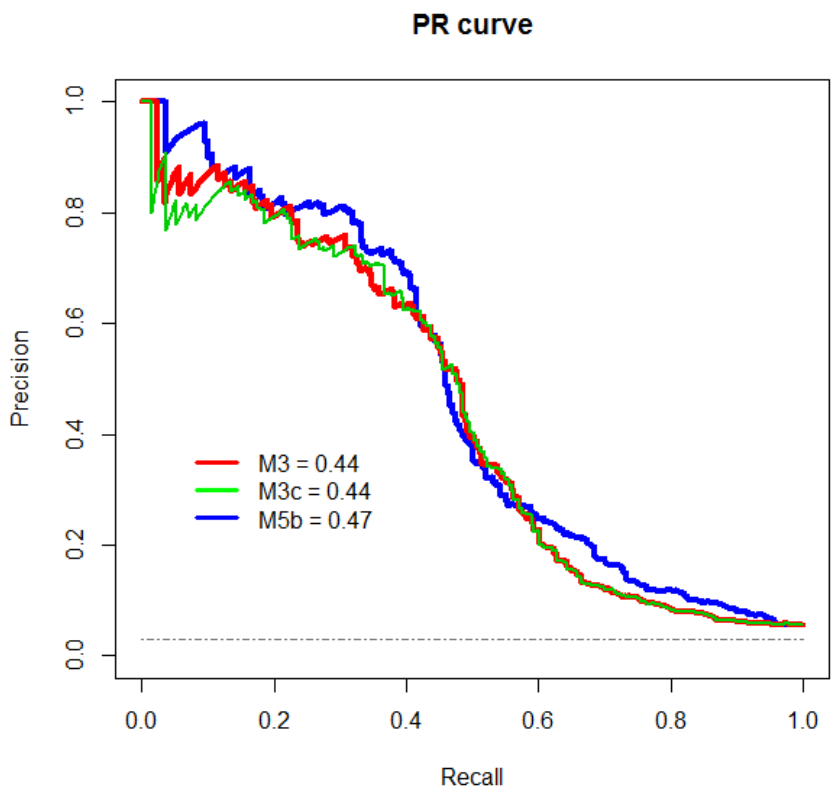
Make N such groups, plot the actual vs the estimated probabilities. A straight line indicate good calibration.

ROC and PR curves – AOF

Receiver operating characteristic (ROC) curve



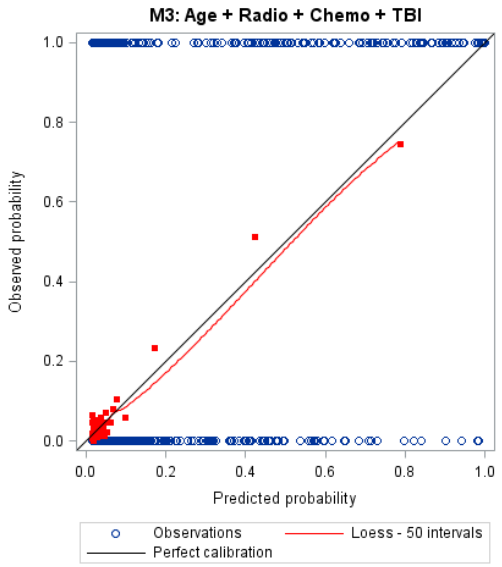
Precision-Recall (PR) curve



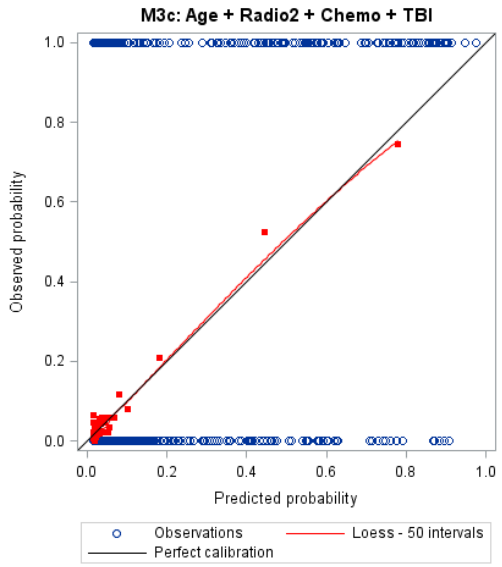
M3: Age + Radio + Chemo + TBI (AUC = 0.78, AP = 0.44)
M3c: Age + Radio2 + Chemo + TBI (AUC = 0.78, AP = 0.44)
M5b: Age + Radio + Chemo + Treatment Era + TBI + Radio*Treatment Era2 (AUC = 0.82, AP = 0.47)

Calibration plot - AOF

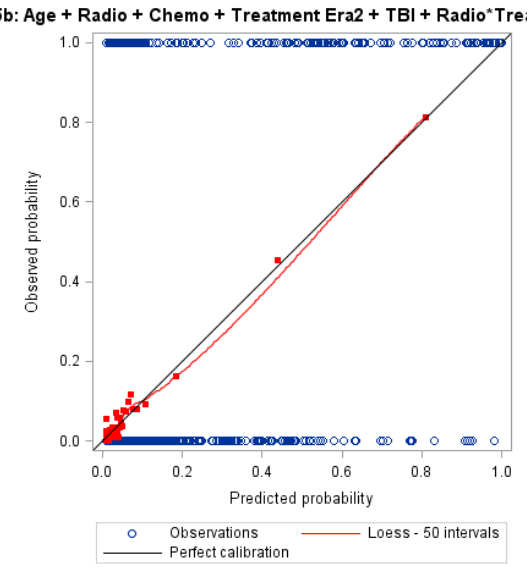
M3: Linear regression



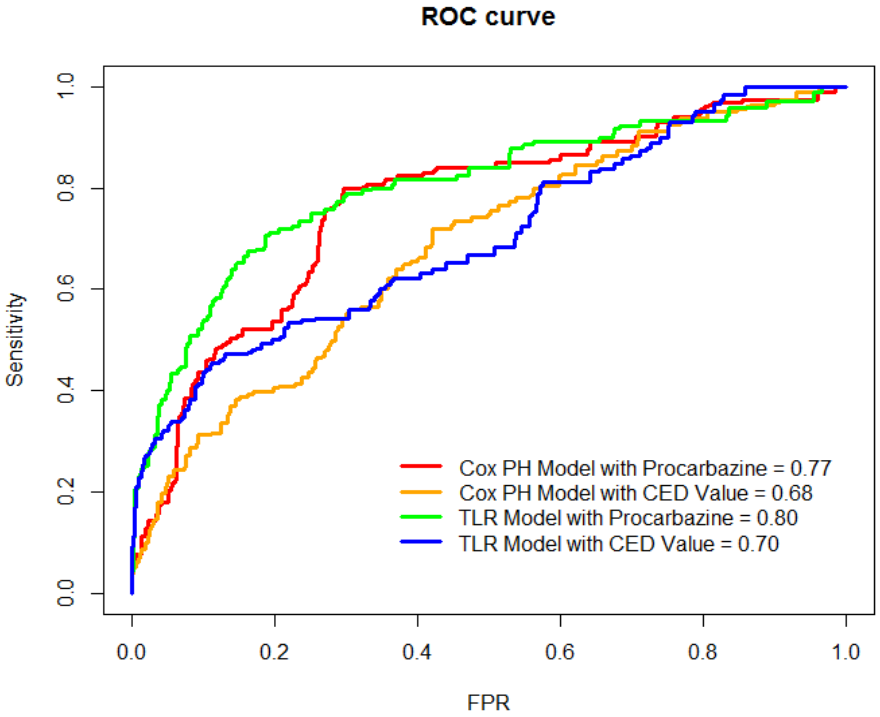
M3c: Piece-wise Linear regression (at 30 Gy)



M5b: With Treatment era2 and interaction



ROC and PR curves – NSPM



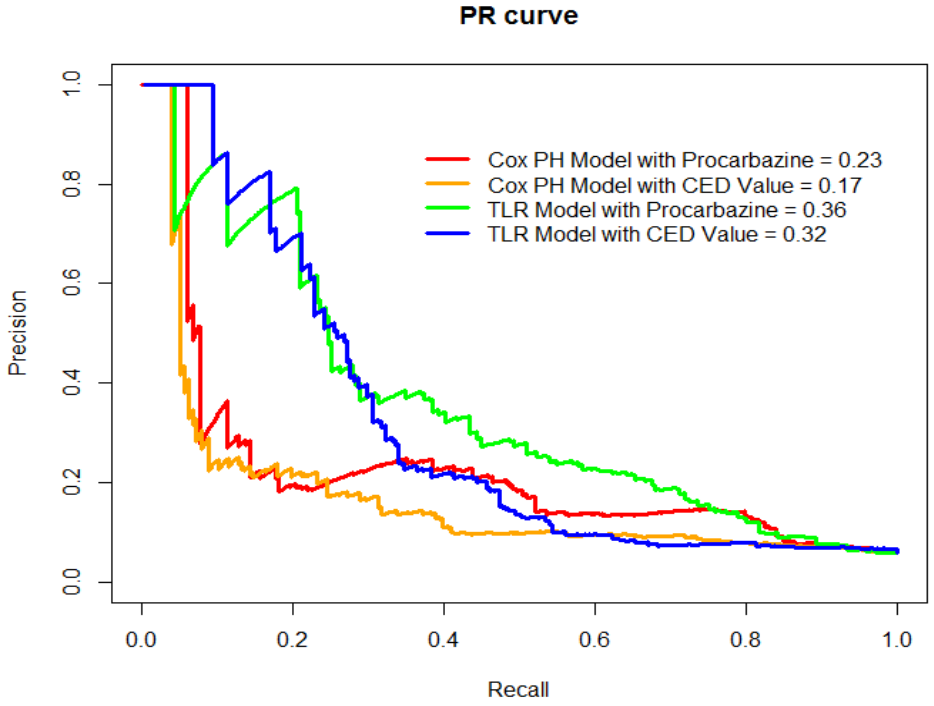


Illustration of Risk Prediction – AOF

Age at Dx	Total body irradiation	Minimum Ovarian Dose (Gy)	CED (g/m2)	Risk of AOF
0	No	No	0.39	<1%
11	No	0.037	7.06	5%
2	No	No	49.84	19.9%
14	Yes	12	2.28	50%
11	Yes	12.6	28.87	76.1%

Illustration of Risk Prediction – NSPM

Age at Dx	Total body irradiation	Minimum Ovarian Dose (Gy)	CED (g/m2)	Risk of NSPM at age 30
18	No	No	No	<1%
14	No	0.088	7.4	5.4%
10	No	12.40	4.1	24.4%
8	Yes	12.00	6.7	61.3%

Future work

- Solving mystery of the treatment period effect
- Dealing with competing risks in modelling NSPM
- Refining prediction models
- Internal validation
- External validation
- Developing application software
- Implementation in clinical settings
- Evaluation

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