

Joint Breast Cancer Registry

SINGAPORE

Report No.2

April 2019



Prepared by

Dr Wong Fuh Yong

Lian Wei Xiang

Dr Wong Ru Xin

On behalf of

Joint Breast Cancer Registry

© Joint Breast Cancer Registry

Information included herein may be used freely for the purpose of education, research or advocacy provided that the Joint Breast Cancer Registry (JBCR) is acknowledged in full. JBCR requests to be informed in writing of all such uses for its record. For copying in any other circumstances, or for re-use in other publications, permission must be secured in writing.

For further information and feedback, please email: wong.fuh.yong@singhealth.com.sg

Foreword

It gives me great pleasure to pen this forward for the 2nd Report of the Joint Breast Cancer Registry (JBCR). This is an excellent collaborative effort by specialists from multiple disciplines across all institutions in SingHealth to build a registry of breast cancer patients. There is tremendous potential to use this data to help inform healthcare providers, the public and policy makers. It will serve as a platform to lobby for resources, as well as to serve as a treasure trove for retrospective review and future planning. I would like to congratulate Dr Wong Fuh Yong, Lian Wei Xiang and Dr Wong Ru Xin as well as all contributors of the JBCR for having put together this important work. This is an excellent example of how we can achieve more when we work together and I am very proud of them.



Prof William Hwang
Medical Director
National Cancer Centre, Singapore

Acknowledgement

We will like to thank the following people who have contributed towards the Joint Breast Cancer Registry and in the preparation of this report.

Chan Junjie Jack	NCC	Ngeow Yuen Yie Joanne	NCC
Chay Wen Yee	NCC	Poh Shuxian Sharon	NCC
Chew Sui Tjien Lita	NCC	Preetha Madhukumar	NCC
Chua Eu Tiong	NCC	Saw Myat Thitsar	NCC
Chua Gail Wan Ying	NCC	Sethi Vijay Kumar	NCC
Dent Rebecca	NCC	Shih Vivianne	NCC
Ho Shihan Bryan	NCC	Sim Yirong	NCC
Jain Amit	NCC	Tan Jing Ying Tira	NCC
Koo Si-Lin	NCC	Tan Kiak Mien Veronique	NCC
Kusumawidjaja Grace	NCC	Tan Kiat Tee Benita	SKH
Lee Guek Eng	NCC	Tan Puay Hoon	SGH
Lee Jie Xin Joycelyn	NCC	Tan Qing Ting	KKH
Lee Jung Ah	KKH	Tan Su Ming	CGH
Li Youquan	NCC	Tan Yia Swam	KKH
Lian Weixiang	NCC	Tan Ying Cong Ryan Shea	NCC
Lim Faye Lynette	NCC	Wong Chow Yin	SGH
Lim Geok Hoon	KKH	Wong Fuh Yong	NCC
Lim Hsuen Elaine	NCC	Wong Mabel	NCC
Lim Sue Zann	SGH	Wong Ru Xin	NCC
Lim Swee Ho	KKH	Wong Su Lin Jill	NCC
Loh Kiley Wei-Jen	NCC	Yap Yoon Sim	NCC
Mo Michelle JiaQi	CGH	Yeo Ming Chert Richard	NCC
Ng Raymond	NCC	Yong Wei Sean	NCC
Ng Wee Loon	NCC		

We also thank the staff of **Department of Cancer Informatics**, NCCS for their help in creating and supporting the Breast Tumour Board software through which a significant amount of data was made available for JBCR as well as the **Division of Radiation Oncology** who has kindly provided manpower support for the curation of this database.

Table of Contents

Foreword.....	I
Acknowledgement.....	II
List of Figures	V
List of Tables	VII
1. Status of the Joint Breast Cancer Registry (JBCR)	1
1.1. Number of cases.....	1
1.2. Completeness of the database.....	2
2. Follow up.....	3
2.1. Status	3
3. Demographics.....	5
3.1. Age at diagnosis	5
3.2. Race	7
3.3. Menopausal Status	10
3.4. Presentation.....	11
4. Tumour Characteristics	13
4.1. Histology.....	13
4.2. Staging	15
4.3. Histology Subtype	19
4.4. Differentiation Grade.....	23
4.5. Tumour Size	25
4.6. Nodal Status	26
5. Treatment.....	28
5.1. Breast Surgery	28
5.2. Chemotherapy	34
5.3. Radiation Therapy.....	38
5.4. Targeted Treatment	43
5.5. Neo-Adjuvant Chemotherapy Treatment.....	46

6.	Survival and Outcomes	47
6.1.	Overall Survival.....	49
6.2.	Disease Free Survival (DFS).....	55
6.3.	Ipsilateral Breast Tumour Recurrence (IBTR)	58
6.4.	Distant Disease Free Survival (DDFS)	60
7.	Non-invasive cancers	63
8.	Research.....	66
8.1.	Published Manuscripts	66
8.2.	Ongoing Studies	67
9.	Reference	68
	APPENDIX: List of variables	A

List of Figures

Figure 1-1. Number of cases by diagnosis year.	1
Figure 1-2. Completeness of the JBCR database.	2
Figure 2-1. Histogram of years of follow up.	3
Figure 3-1. Histogram of age at diagnosis.	5
Figure 3-2. Boxplot of age by diagnosis year category.	6
Figure 3-3. Proportion of cases by race in different cohorts.	7
Figure 3-4. Distribution of age at diagnosis by race in different cohorts.	8
Figure 3-5. Distribution of patients' race by age group in different cohorts.	9
Figure 3-6. Distribution of patients' menopausal status by race.	10
Figure 3-7. Distribution of presentation type by age group.	11
Figure 3-8. Distribution of presentation type by race.	12
Figure 4-1. Percentage of cases by anatomic and prognostic staging as per AJCC8.	16
Figure 4-2. Distribution of anatomic stage by race.	16
Figure 4-3. Distribution of anatomic stage by age group.	17
Figure 4-4. Percentage of cases by anatomic stage by presentation type.	17
Figure 4-5. Distribution of anatomic stage by histology subtype.	18
Figure 4-6. Percentage of cases by histology subtype.	20
Figure 4-7. Distribution of histology subtype by race.	21
Figure 4-8. Distribution of histology subtype by age group.	21
Figure 4-9. Distribution of histology subtype by grade differentiation.	22
Figure 4-10. Percentage of cases by histology subtype by presentation status.	22
Figure 4-11. Percentage of cases by grade differentiation.	23
Figure 4-12. Percentage of cases by grade differentiation by presentation type.	24
Figure 4-13. Distribution of grade differentiation by race.	24
Figure 4-14. Histogram of tumour size.	25
Figure 4-15. Percentage of cases by nodal stage group.	26
Figure 4-16. Percentage of cases by nodal stage by presentation type.	27
Figure 4-17. Percentage of patients receiving chemotherapy by nodal stage.	27
Figure 5-1. Percentage of cases by overall surgery type.	29
Figure 5-2. Percentage of cases with reconstruction.	30
Figure 5-3. Distribution of surgery type by race.	31
Figure 5-4. Distribution of surgery type by age group.	32
Figure 5-5. Distribution of surgery type by anatomic staging.	32
Figure 5-6. Distribution of surgery type by tumour size.	33

Figure 5-7. Proportion of surgery type by diagnosis year.	33
Figure 5-8. Proportion of patients who received chemotherapy.	34
Figure 5-9. Distribution of drugs for patients who received chemotherapy.	35
Figure 5-10. Percentage of patients receiving chemo by race.	36
Figure 5-11. Percentage of patients who received chemotherapy by anatomic staging.	36
Figure 5-12. Percentage of patients who received chemotherapy by histology subtype.	37
Figure 5-13. Proportion of radiation therapy techniques received by patients.	38
Figure 5-14. Proportion of techniques used by patients by diagnosis year.	39
Figure 5-15. Proportion of hypo fractionation regimes received by patients by diagnosis year.	40
Figure 5-16. Proportion of patients receiving radiation therapy by surgery type and age group.	41
Figure 5-17. Proportion of patients receiving radiation therapy by surgery type and anatomic stage group.	42
Figure 5-18. Distribution of radiation therapy field that patients received by surgery type and anatomic stage group.	42
Figure 5-19. Proportion of patients who received targeted treatment by treatment year.	43
Figure 5-20. Use of targeted therapy in patients who are HER2 positive and had chemotherapy by treatment year.	44
Figure 5-21. Uptake of targeted therapy in patients who are node positive or had chemotherapy by treatment year.	44
Figure 5-22. Distribution of patients who received targeted therapy by anatomic staging.	45
Figure 5-23. Proportion of patients who received neo-adjuvant treatment by treatment year.	46
Figure 6-1. Snapshots of the online survival calculator. (a) Selection Criteria for outcomes estimation. (b) Survival curve of matched population. (c) Icon array for easy visual interpretation of outcomes.	48
Figure 6-2. Overall survival by race.	49
Figure 6-3. Overall survival by anatomic stage group.	50
Figure 6-4. Overall survival by histology subtype.	51
Figure 6-5. Overall survival by tumour size group.	52
Figure 6-6. Overall survival by nodal stage.	53
Figure 6-7. Overall survival by grade differentiation.	54
Figure 6-8. Disease free survival by age group.	55
Figure 6-9. Disease free survival by race.	56
Figure 6-10. Disease free survival by histology subtype.	57

Figure 6-11. Ipsilateral breast tumour recurrence by tumour stage.....	58
Figure 6-12. Ipsilateral breast tumour recurrence by histology subtype.....	59
Figure 6-13. Distant disease free survival by nodal stage.	60
Figure 6-14. Distant disease free survival by histology subtype.	61

List of Tables

Table 2-1. Summary statistics of all patients who have follow ups.....	3
Table 2-2. Percentage of cases by follow up years.	3
Table 3-1. Summary statistics of age at diagnosis.	5
Table 3-2. Proportion of cases by menopausal status.....	10
Table 3-3. Proportion of cases by presentation status.....	11
Table 4-1. Distribution of cases by anatomic and prognostic staging as per AJCC8.	15
Table 4-2. Distribution in hormone receptor status.	19
Table 4-3. Proportion of cases by histology subtype.	19
Table 4-4. Proportion of cases by grade differentiation.	23
Table 4-5. Summary statistics for tumour size.....	25
Table 4-6. Percentage of cases by nodal status.....	26
Table 5-1. Percentage of cases by overall surgery type.....	28
Table 5-2. Percentage of cases by reconstruction type.....	30
Table 6-1. Definition of the survival end points.....	47

New in the Second Report

- Inclusion of Changi General Hospital and Sengkang General Hospital
- Analyses on Singapore residents only (i.e. Singapore Citizens and Permanent Residents)
- Trend of incidence of breast cancer cases reported over the years
- Prognostic staging of breast cancer patients based on the new AJCC 8th Breast Cancer Staging Manual
- Chemotherapy drug classification received by patients
- Radiotherapy modality
- Survival analyses in non-invasive cancers
- Optimized scaling in axes for the Kaplan Meir survival plots for readability

1. Status of the Joint Breast Cancer Registry (JBCR)

1.1. Number of cases

Approximately **26,000** breast cancer cases which were managed in Changi General Hospital, KK Women and Children Hospital, National Cancer Centre Singapore, Sengkang General Hospital and Singapore General Hospital between 1960 and 2017 were included in the JBCR.

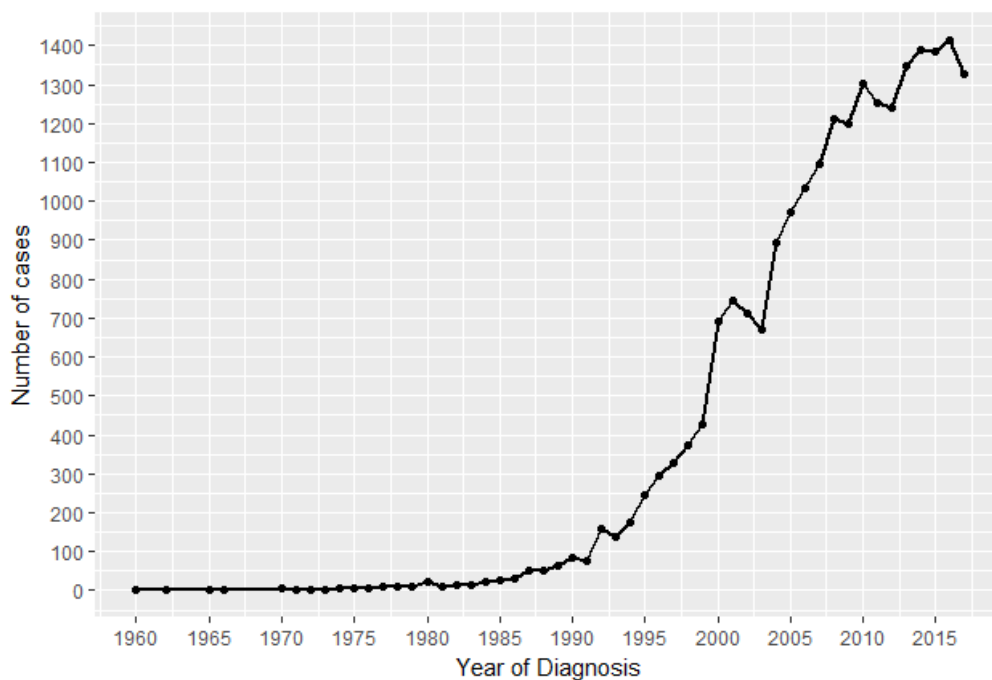


Figure 1-1. Number of cases by diagnosis year.

1.2. Completeness of the database

Completed cases are defined by patients with complete information of the following variables:

- 1) Name
- 2) National Registration Identity Card (NRIC)
- 3) Date of birth
- 4) Date of diagnosis
- 5) Pathological tumour stage
- 6) Pathological nodal stage
- 7) Pathological metastatic stage
- 8) Estrogen receptor status
- 9) Progesterone receptor status

Note: HER2 status is available for 91% of patients diagnosed after 2006.

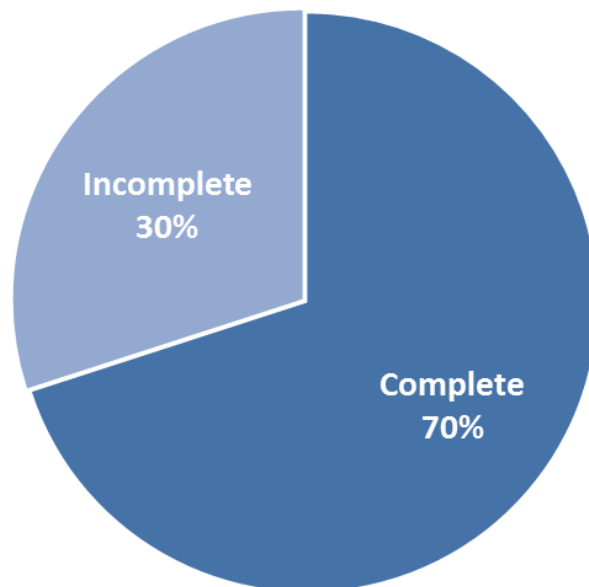


Figure 1-2. Completeness of the JBCR database.

2. Follow up

2.1. Status

The median follow up is 5.0 years (Table 2-1). Approximately 76% of the patient cohort has a follow up of at least 2 years.

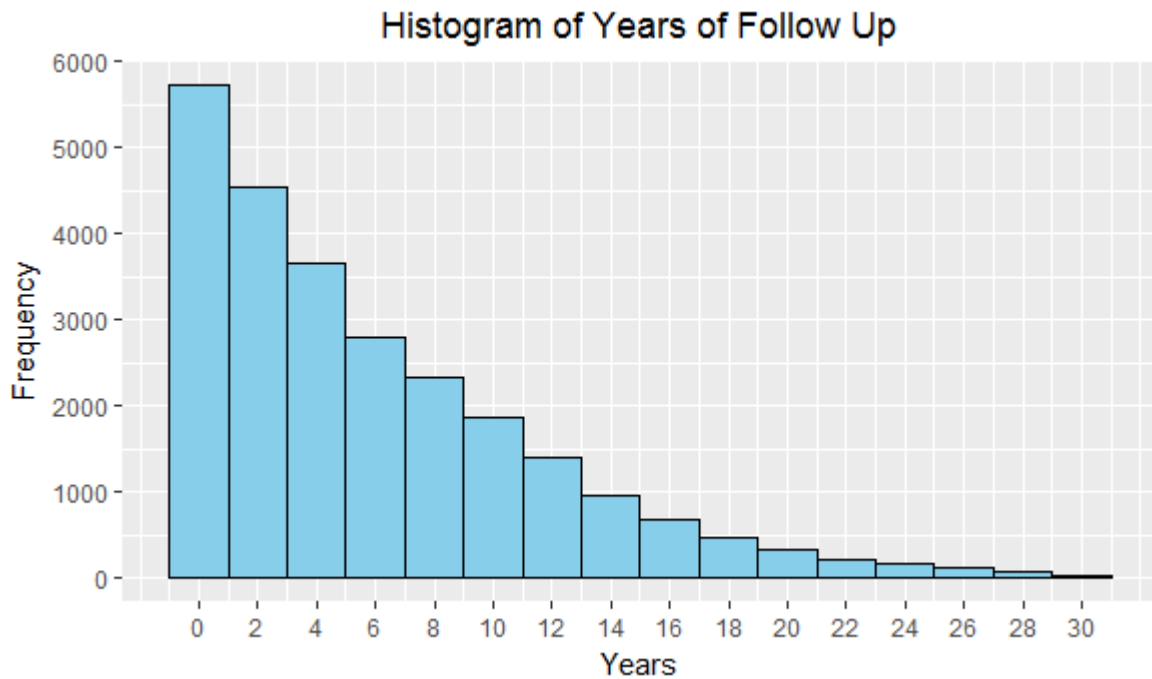


Figure 2-1. Histogram of years of follow up.

Table 2-1. Summary statistics of all patients who have follow ups.

Population Size	Mean (years)	Standard Deviation	Median (years)	1 st Quartile	3 rd Quartile	Mode	Minimum	Maximum
25,000	6.3	5.8	5.0	2.0	9.0	1.0	0	30

Table 2-2. Percentage of cases by follow up years.

Follow up years	Frequency	Percentage(%)
≥ 2	20,000	76
≥ 5	13,000	51
≥ 10	6,400	25

≥ 15	2,700	10
-----------	-------	----

- [INVASIVE BREAST CANCER] -

For clarity, patients with invasive breast cancers are presented separately from those with non-invasive disease (Section 3 to 6). All values are rounded to 2 significant figures.

3. Demographics

3.1. Age at diagnosis

Overall, the mean age at diagnosis is 54 years. It has been increasing over the years, starting from an average of 36 years before the 1970s to 56 years in this current decade.

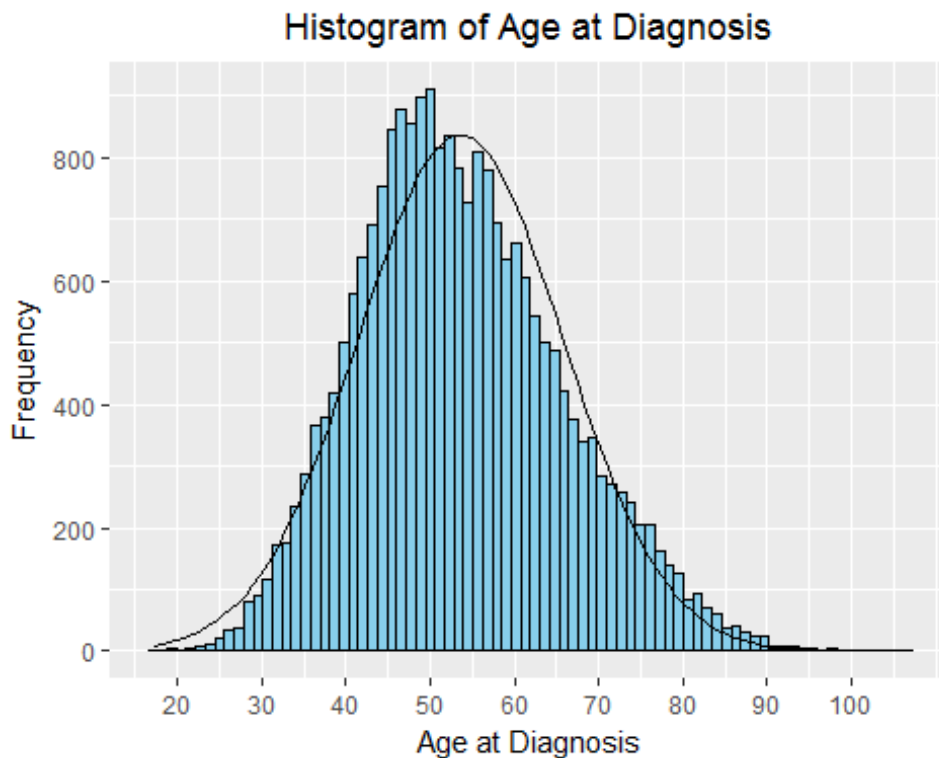


Figure 3-1. Histogram of age at diagnosis.

Table 3-1. Summary statistics of age at diagnosis.

Population Size	Mean (years)	SD	Median (years)	1 st Quartile	3 rd Quartile	Minimum	Maximum
23,000	54	12	52	45	61	18	110

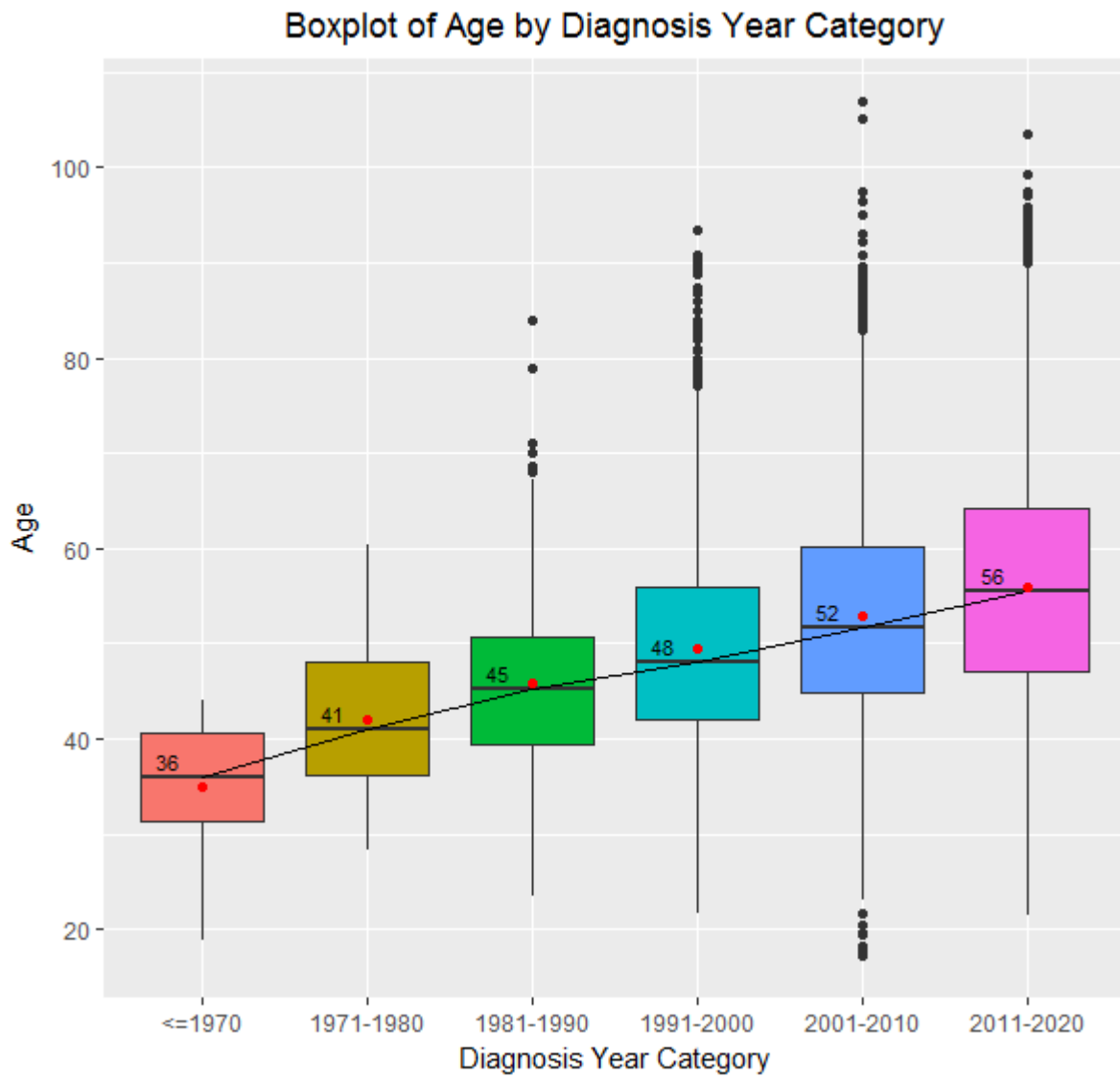


Figure 3-2. Boxplot of age by diagnosis year category.

3.2. Race

About 17% of the database consists of foreign patients treated in participating institutions. In this report, we are presenting data of resident patients separately whenever possible in order to better represent the nature of the disease, its treatment and patient outcomes.

With this adjustment, the proportion of patients by race in JBCR is more reflective of that in the general population. In comparison with the general demographics of Singapore in 2017 (Department of Statistics Singapore, 2018), the proportion of Malays and other races were consistent. JBCR has a higher proportion of Chinese patients (81% vs 74%) and fewer Indians patients (5.4% vs 9.0%) (Figure 3-3) (Department of Statistics Singapore, 2018).

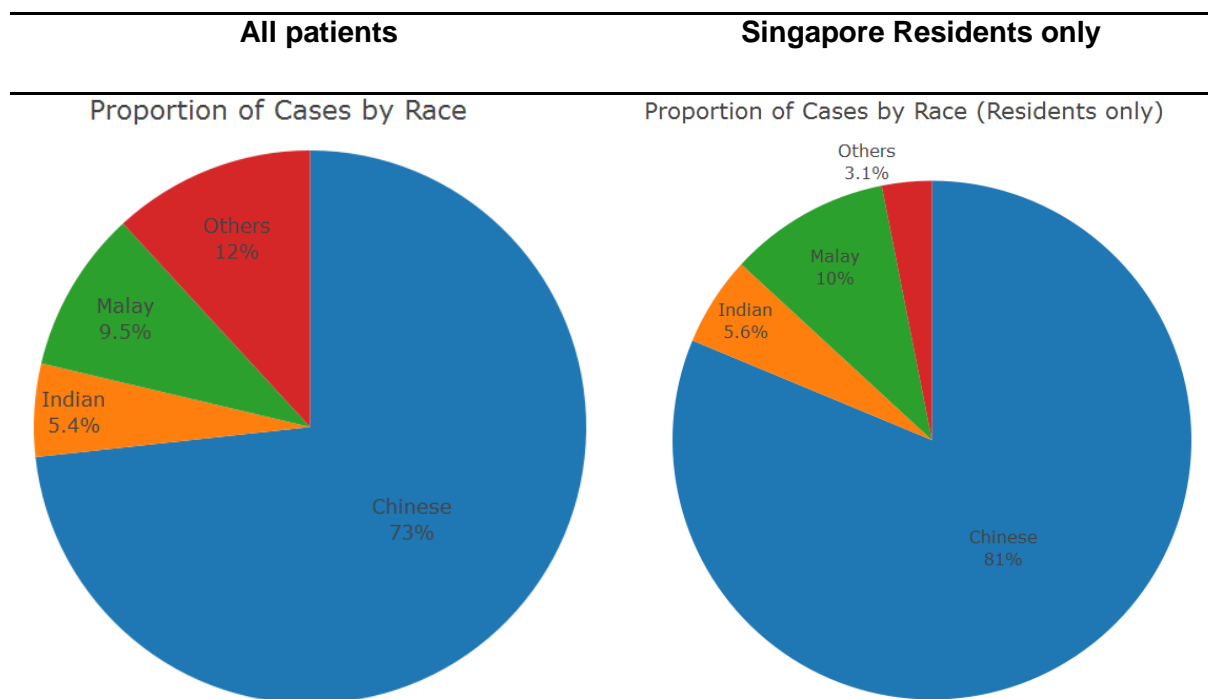


Figure 3-3. Proportion of cases by race in different cohorts.

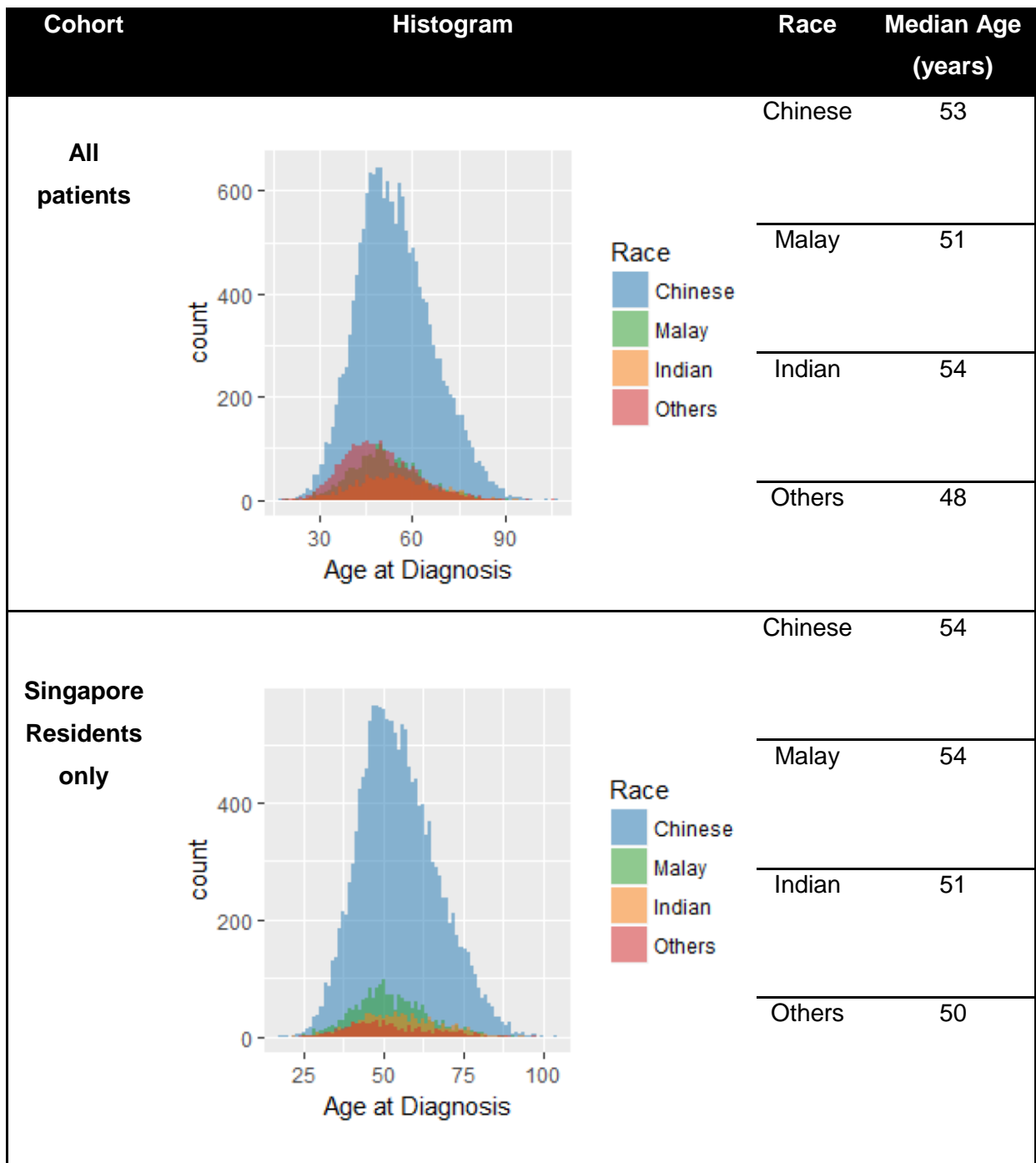


Figure 3-4. Distribution of age at diagnosis by race in different cohorts.

Among the 3 major races in Singapore, Malays are diagnosed with breast cancer at the youngest age at a median age at 51 years in the entire cohort. However among the residents, the Indians are diagnosed at a younger age at about 51 years (Figure 3-4).

Cohort Graph

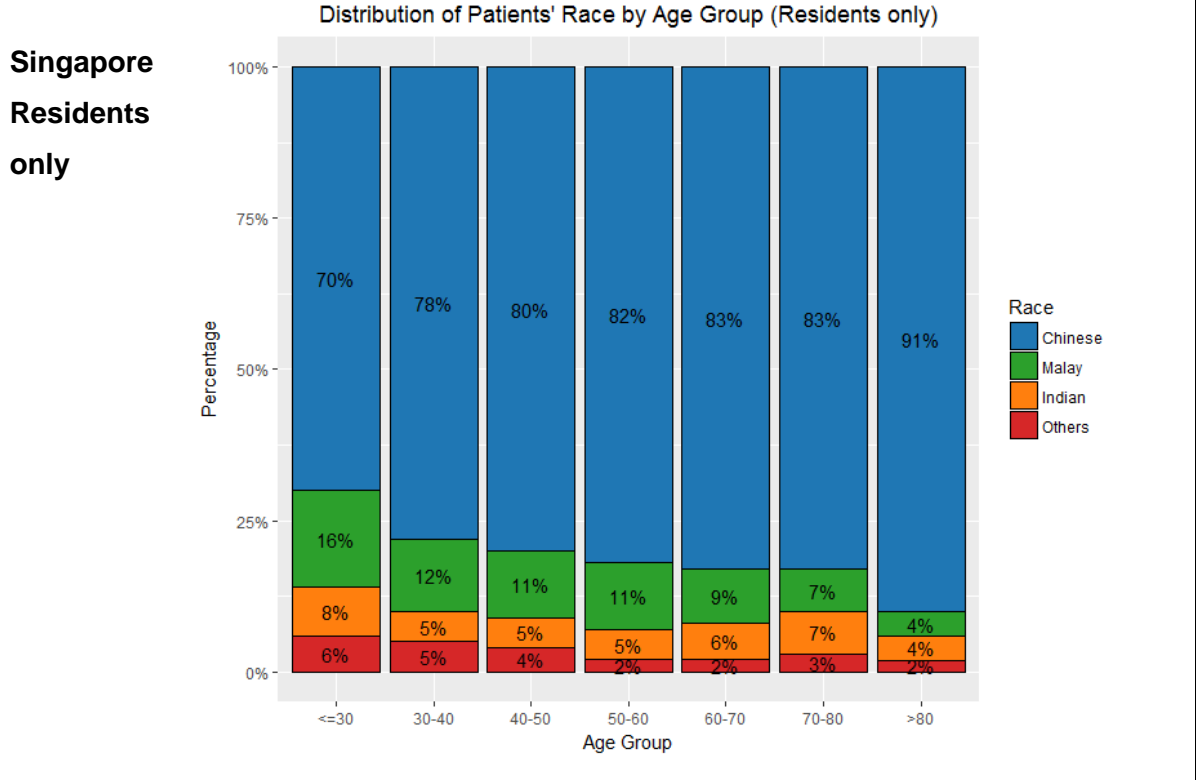
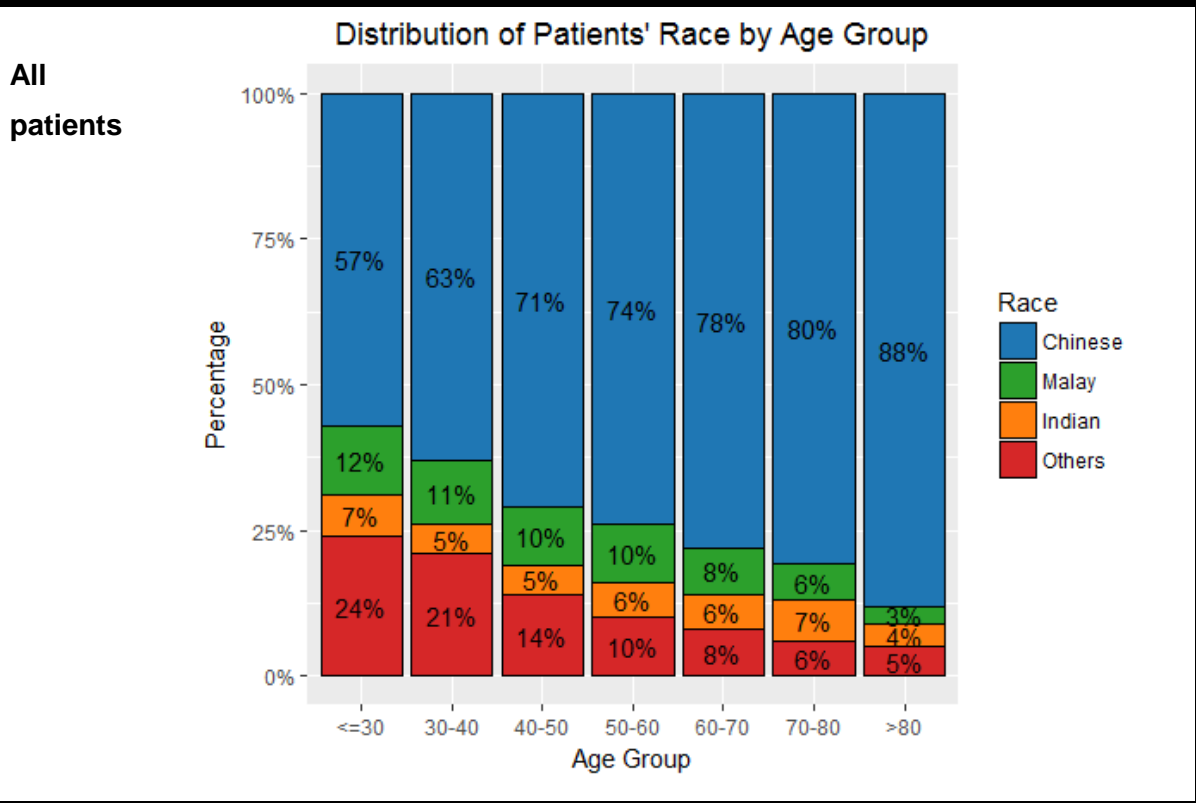


Figure 3-5. Distribution of patients' race by age group in different cohorts.

As the age group increases, there are proportionately more Chinese and fewer Malays (Figure 3-5).

- [In the following analyses, only Singapore residents are analysed] -

3.3. Menopausal Status

Not accounting for unknown data, the majority of patients are post-menopausal (Table 3-2). Of the 3 major races in Singapore, the proportion of pre-menopausal patients is the highest among the Malays at 43%, compared to 34% for Chinese and 34% for Indians.

Table 3-2. Proportion of cases by menopausal status.

	Frequency	Percentage (%)
Not Applicable	10	11
Peri	580	5.0
Post	6,700	59
Pre	4,000	35
Pregnancy-related	50	0.41

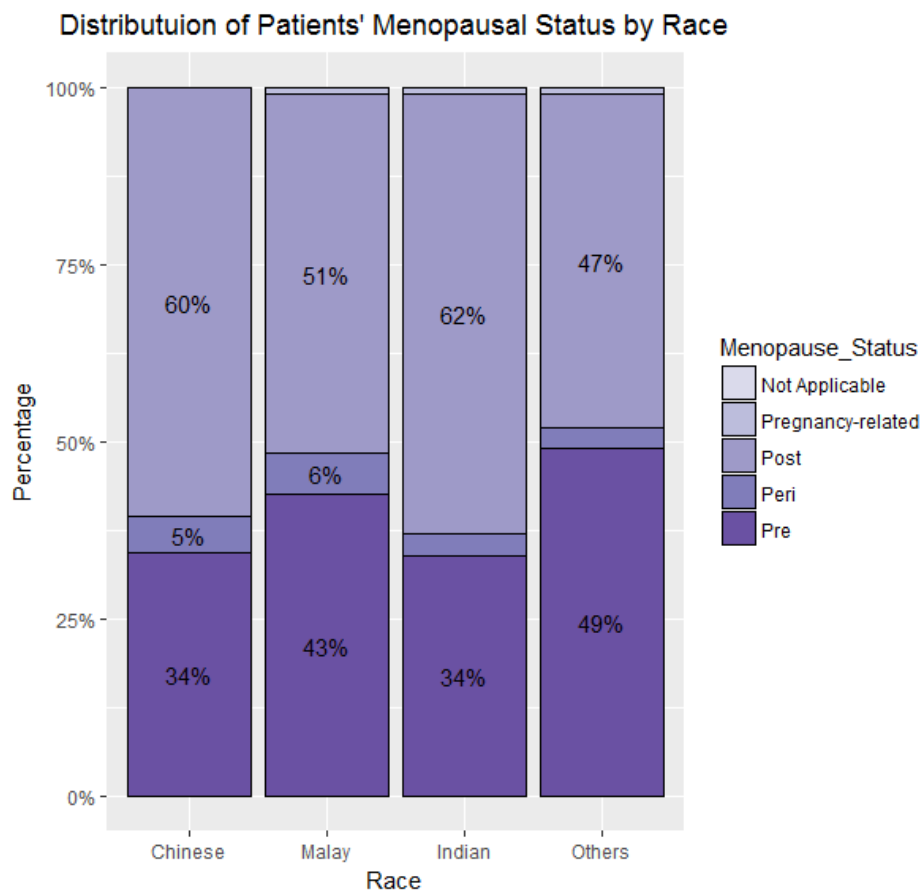


Figure 3-6. Distribution of patients' menopausal status by race.

3.4. Presentation

Of the patients with known mode of presentation, 5,700 had clinically detectable cancers while the other 1,400 patients were screen-detected. The proportion of screen-detected cancer is the highest among age group between 50 and 70 years (Figure 3-7). This is in line with the screening programme in Singapore to encourage women to go for regular breast screening every 2 years between 50 and 69 years (Cancer Screening, 2010). The second highest group for screen-detected cancer belongs to the age group between 40 and 50 years (Figure 3-7). This could be due to greater awareness of women in this age group on breast cancer screening even though such examination is non-mandatory (Cancer Screening, 2010). Malays had the lowest proportion of screened cancer at 12%, compared to 20% in both the Chinese and Indians each.

Table 3-3. Proportion of cases by presentation status.

	Frequency	Percentage (%)
Clinical	5,700	81
Radiological	1,400	19

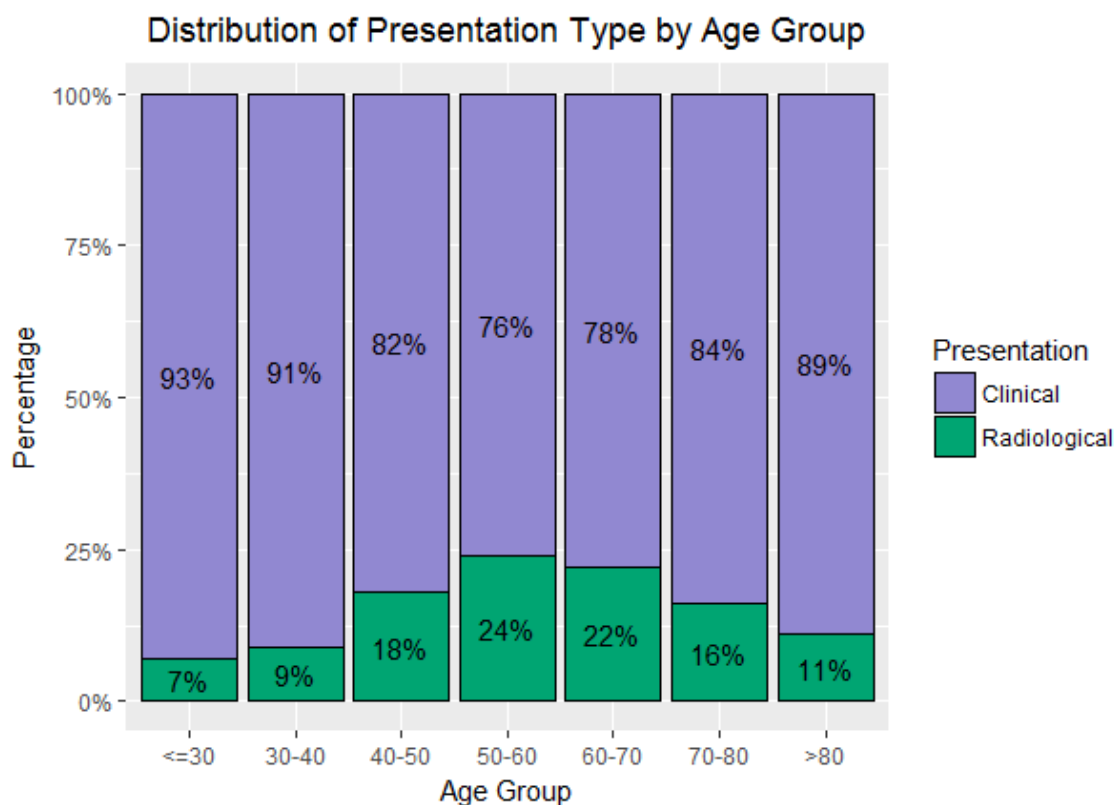


Figure 3-7. Distribution of presentation type by age group.

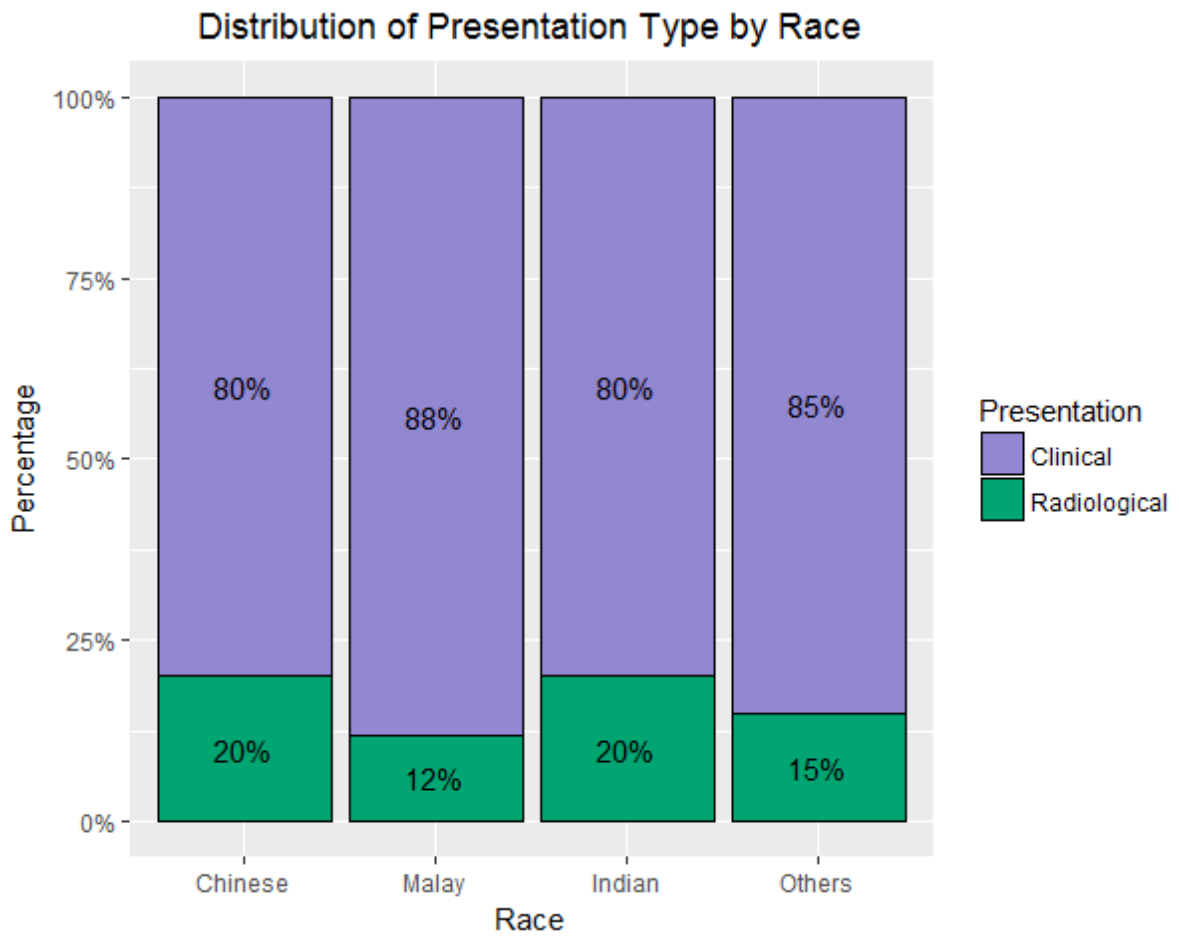


Figure 3-8. Distribution of presentation type by race.

4. Tumour Characteristics

4.1. Histology

With the exclusion of non-invasive cancers, the most common invasive histology is Infiltrative Ductal Carcinoma (IDC), making up 80% of all the histology subtypes.

Histology	Frequency	Percentage (%)
Infiltrative ductal (IDC)	15,000	84
Infiltrative lobular (ILC)	950	5.3
Mucinous carcinoma	510	2.9
Invasive carcinoma NOS	420	2.4
Mixed Ductal lobular carcinoma	210	1.2
Tubular carcinoma	130	0.7
Others	110	0.63
Phyllodes tumor	110	0.59
Medullary carcinoma	92	0.52
Metaplastic carcinoma	89	0.5
Mixed invasive micropapillary ductal carcinoma	26	0.15
Mixed Ductal mucinous carcinoma	23	0.13
Apocrine adenocarcinoma	22	0.12
Neuroendocrine carcinoma	19	0.11
Tubular mixed carcinoma	14	0.08
Infiltrative cribriform carcinoma	12	0.07
Adenoid Cystic Carcinoma	9	0.05
Paget's disease of the breast (only)	9	0.05
Adenosquamous carcinoma	8	0.04
Invasive tubulolobular carcinoma	7	0.04
Lobular carcinoma in-situ (LCIS)	8	0.04
Squamous cell carcinoma	8	0.04
Unknown	7	0.04
Malignant Cystosarcoma Phyllodes	5	0.03
Mixed Ductal tubular carcinoma	6	0.03
Invasive secretory carcinoma	4	0.02
Adenomyoepithelioma	1	0.01

Histology	Frequency	Percentage (%)
Mixed medullary-ductal carcinoma	1	0.01
Muroid carcinoma	1	0.01

4.2. Staging

The AJCC 8th edition staging system was introduced into official use in January 2018. This updated staging system retains an “Anatomic staging” that is similar to the preceding AJCC 7th edition. It further includes a new “Prognostic staging” system which incorporates biological risk factors including tumour differentiation and receptor status on top of the existing anatomic staging (*Hortobagyi, et al., 2018*).

Under both anatomic and prognostic classification, the majority of patients were early staged (stages I and II) at presentation which accounts to about 70% and 78% respectively (*Table 4-1*). However, there is a major change in the distribution of cancer stages under the prognostic system, especially for the early stages. The percentage of Stage I patients under the prognostic staging increases to more than half of the resident cohort while that for Stage II patients decreases to about 20% in the same cohort (*Figure 4-1*). It is likely that the majority of the Stage II patients under the anatomic classification were down-staged to Stage I under the prognostic classification. We have compared the performance of the 7th vs the 8th AJCC staging system and found slightly better discrimination (*Wong et al., 2018*).

Table 4-1. Distribution of cases by anatomic and prognostic staging as per AJCC8.

Staging	Anatomic	Prognostic
Stage I	5,200 (31%)	7,600 (59%)
Stage II	6,700 (39%)	2,500 (19%)
Stage III	3,300 (19%)	1,700 (13%)
Stage IV	1,800 (11%)	1,100 (9%)

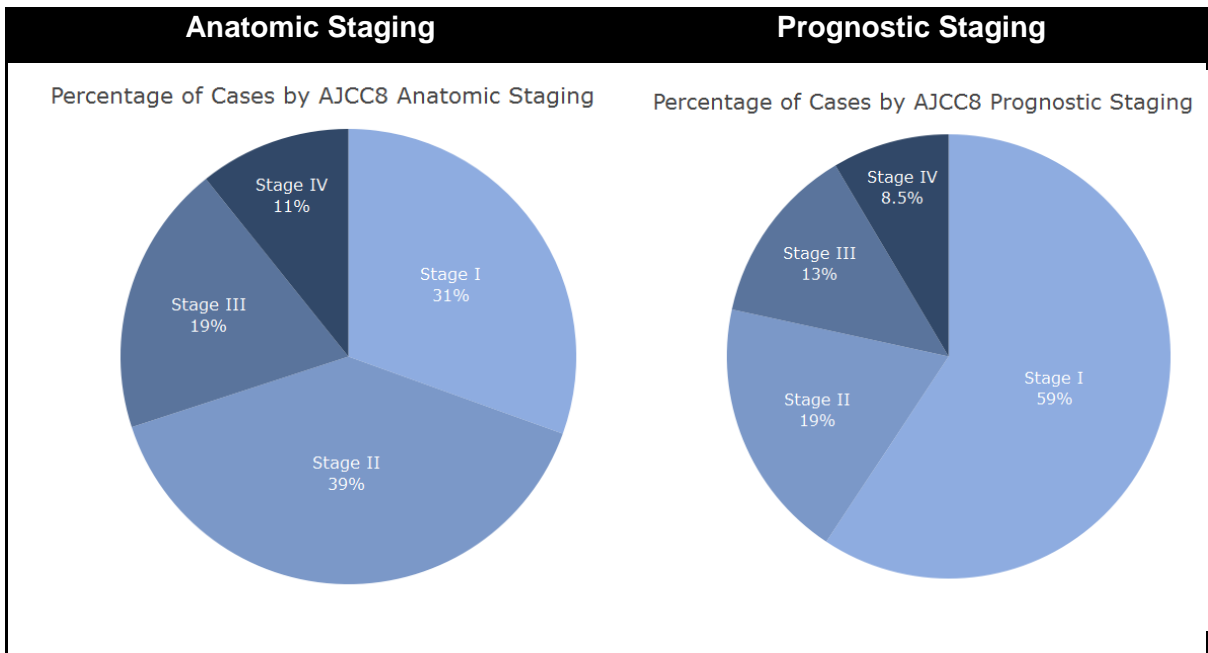


Figure 4-1. Percentage of cases by anatomic and prognostic staging as per AJCC8.

Within each of the 3 major race groups in Singapore, the Malays have the highest proportion of late-staged tumours (Stages III and IV) at 47%, compared to 34% in the Indians and 28% in the Chinese (Figure 4-2).

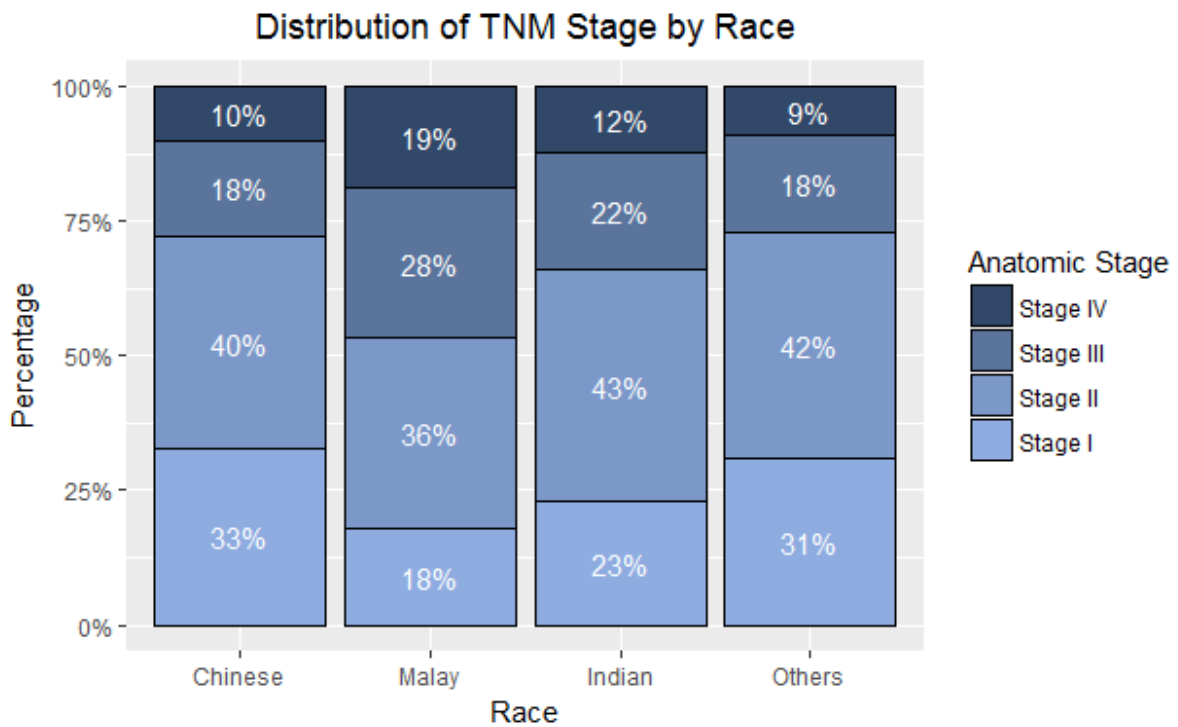


Figure 4-2. Distribution of anatomic stage by race.

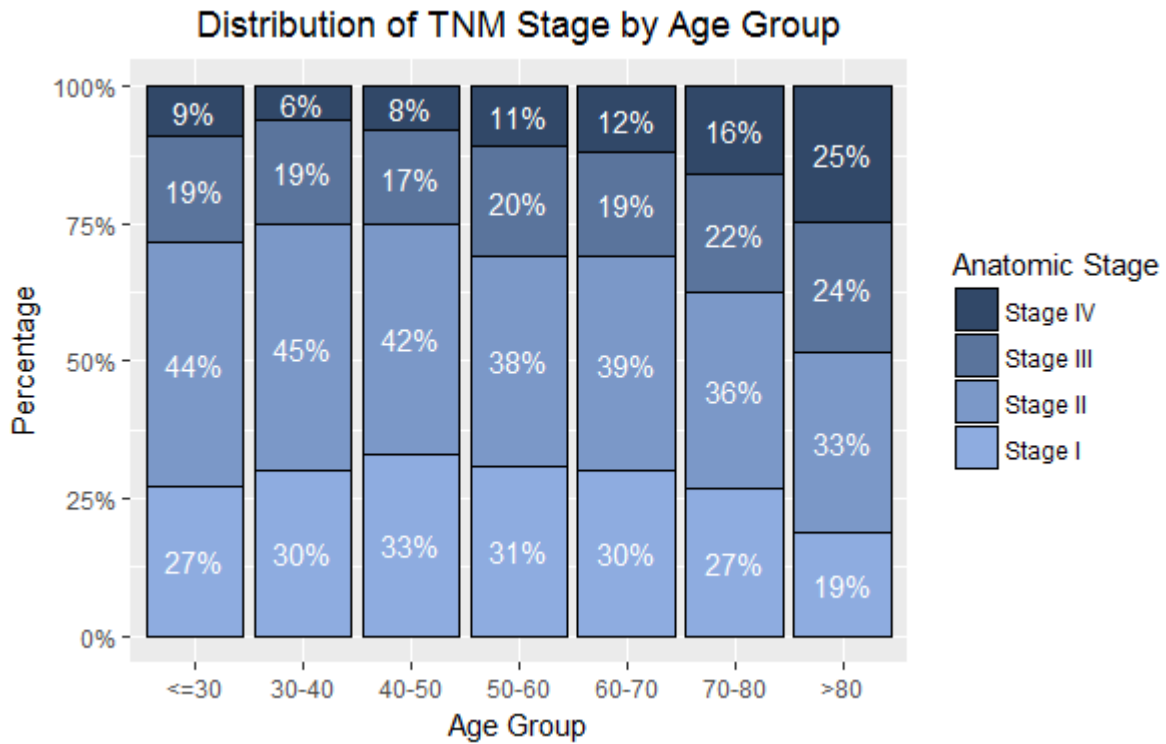


Figure 4-3. Distribution of anatomic stage by age group.

More than half of the screened tumours were stage I compared to only 24% of clinically detected cancers (Figure 4-4).

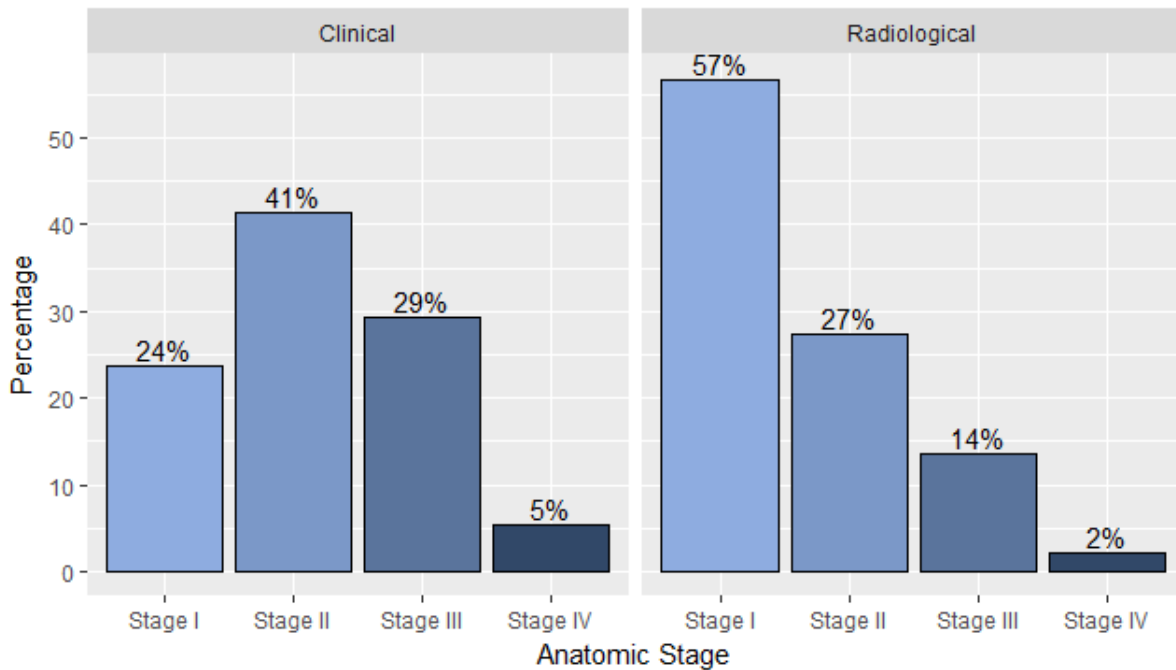


Figure 4-4. Percentage of cases by anatomic stage by presentation type.

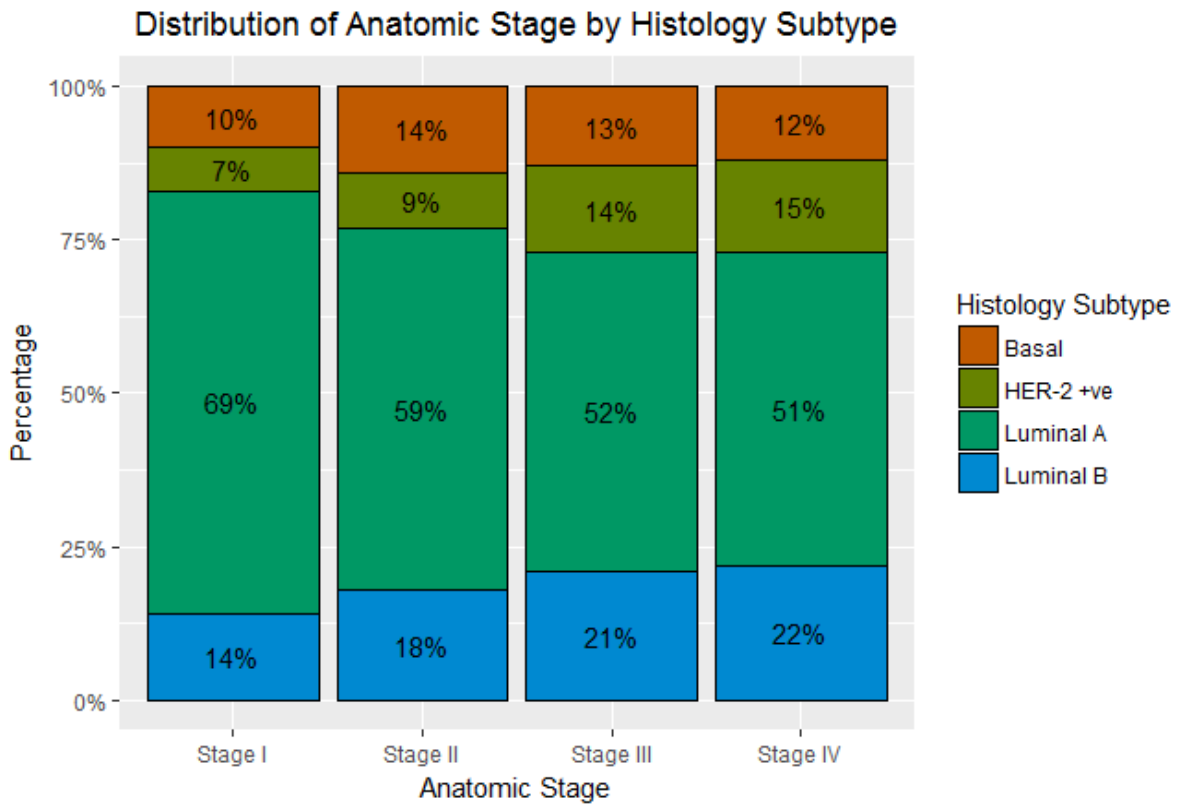


Figure 4-5. Distribution of anatomic stage by histology subtype.

4.3. Histology Subtype

Histology subtype adopts the definition from Goldhirsch, A, et al., 2011 and is described in Table 4-3. Overall, we are not able to classify the histology subtype of 22% of patients due to the non-availability of HER-2 status in patients before 2006. Among those patients with known histology subtypes, luminal A subtype is the most prevalent, accounting for about 60%, followed by luminal B at 18% (Figure 4-6). Triple negative breast cancer patients made up 12% of patients and HER-2 enriched breast cancers the remaining 10%.

Table 4-2. Distribution in hormone receptor status.

Hormone Receptor	Hormone Receptor Status	
	Positive	Negative
ER	11,000 (74%)	3,900 (26%)
PR	9,300 (62%)	5,600 (38%)
HER2	4,100 (30%)	9,900 (70%)

Table 4-3. Proportion of cases by histology subtype.

Histology Subtype	Definition	Frequency	Percentage
Basal	ER, PR and HER-2 negative	1,800	12
HER-2 +ve	ER and PR negative, HER-2 positive	1,500	10
Luminal A	ER or PR positive, HER-2 negative	9,000	60
Luminal B	ER or PR positive, HER-2 positive	2,600	18

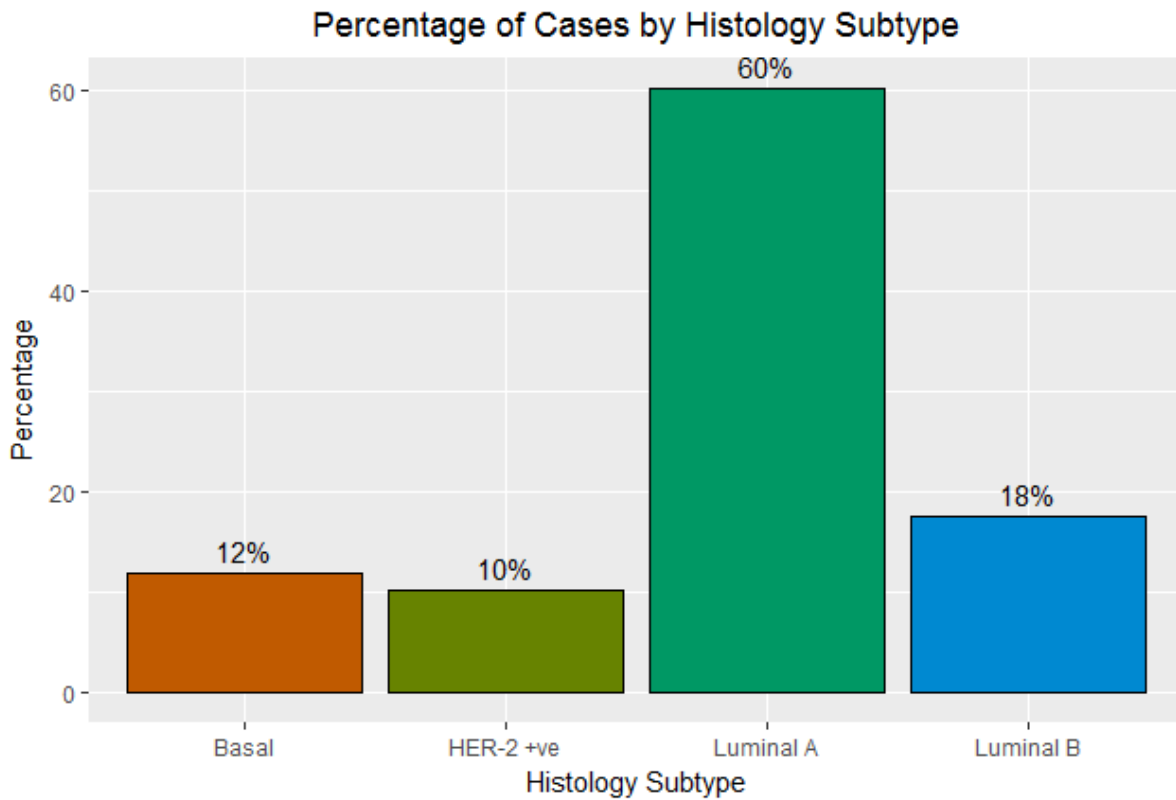


Figure 4-6. Percentage of cases by histology subtype.

Within each of the 3 major races in Singapore, the Chinese have the highest proportion of luminal A at 61%, compared to 56% and 59% in the Malays and Indians respectively (Figure 4-7). Basal cancers are more common in younger patients (Figure 4-8).

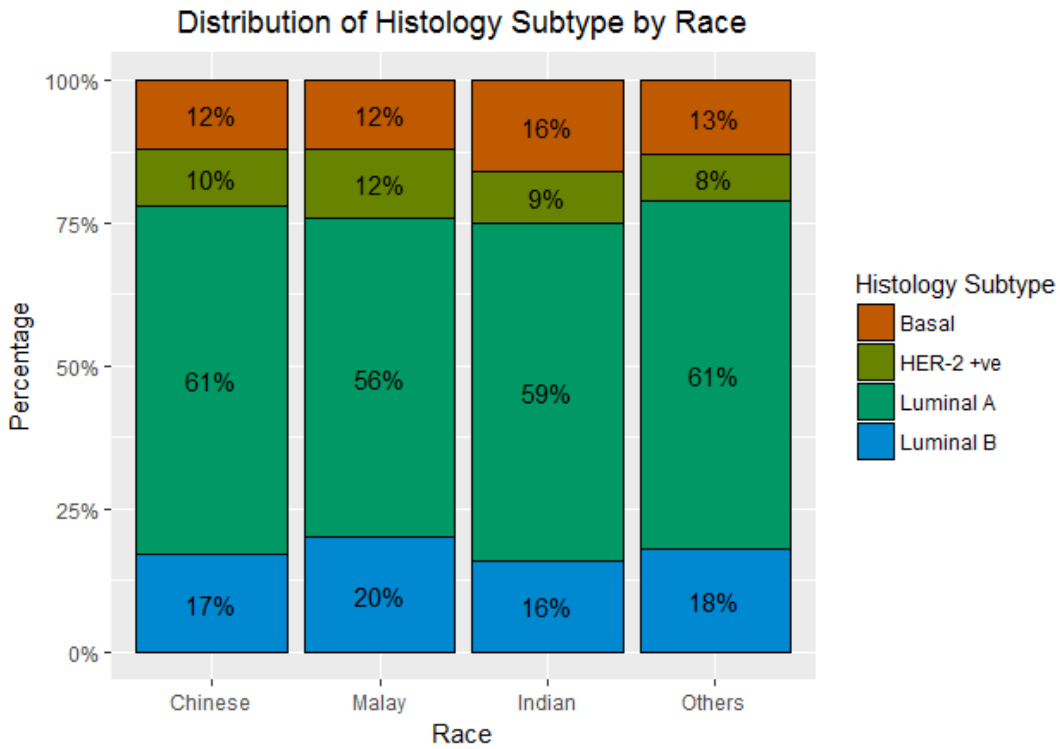


Figure 4-7. Distribution of histology subtype by race.

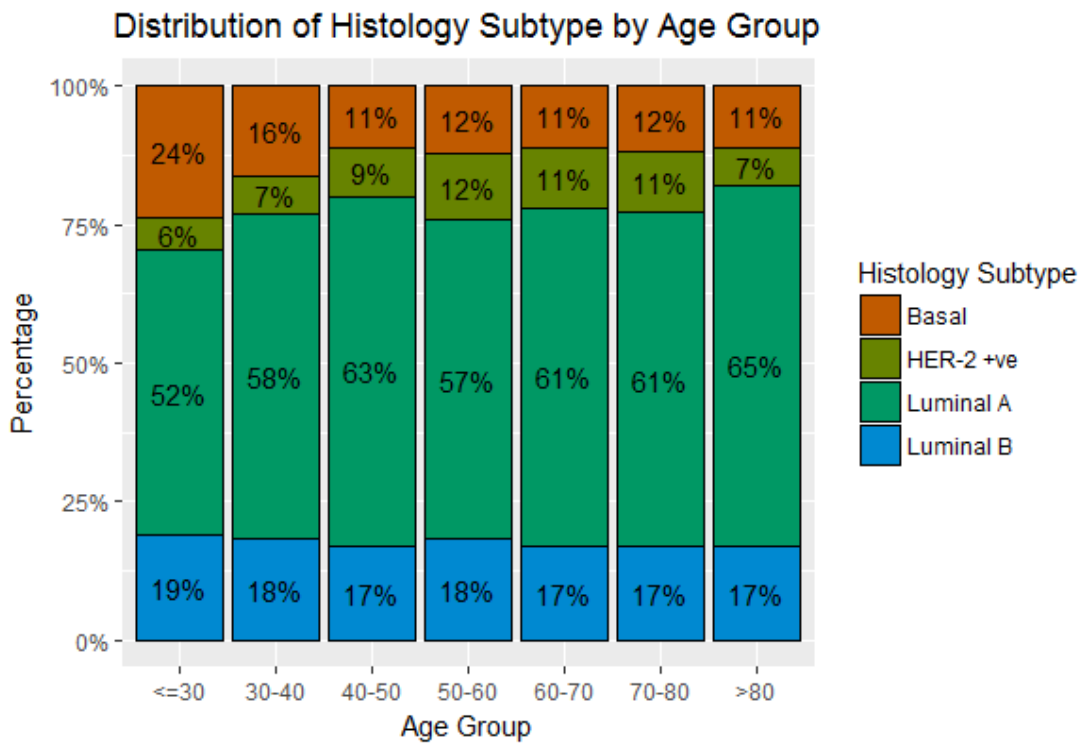


Figure 4-8. Distribution of histology subtype by age group.

As expected, luminal A and B subtypes are highly represented in lower grades of tumour (91% in Grade 1 and 89% in Grade 2) (Figure 4-9). Screened tumours are more indolent with 71% being luminal A as compared to 60% of that in clinically detected cancers (Figure 4-10).

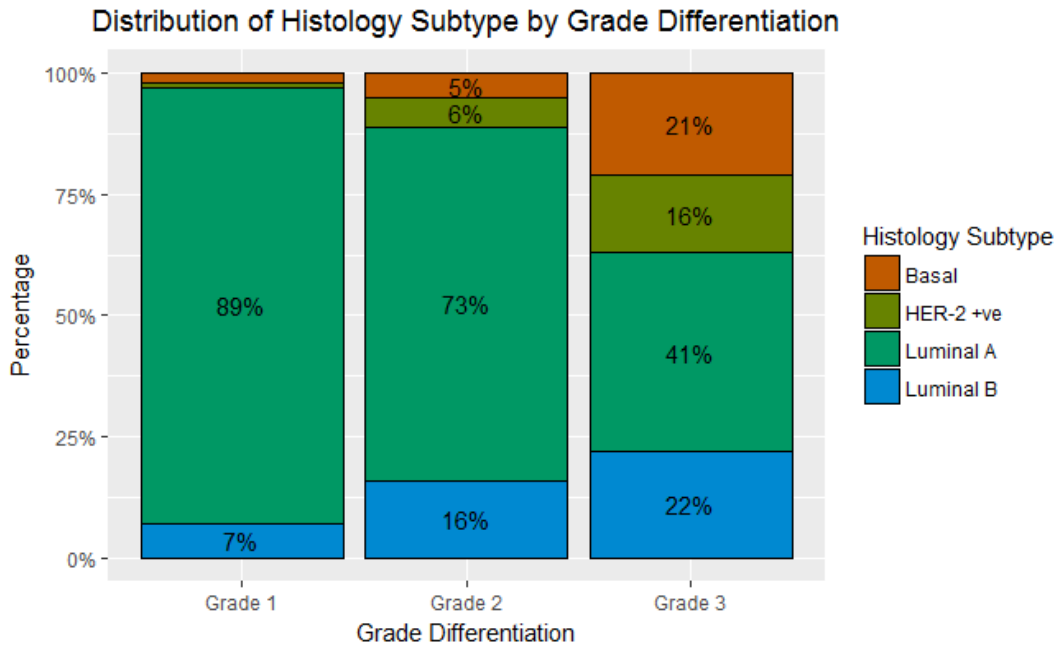


Figure 4-9. Distribution of histology subtype by grade differentiation.

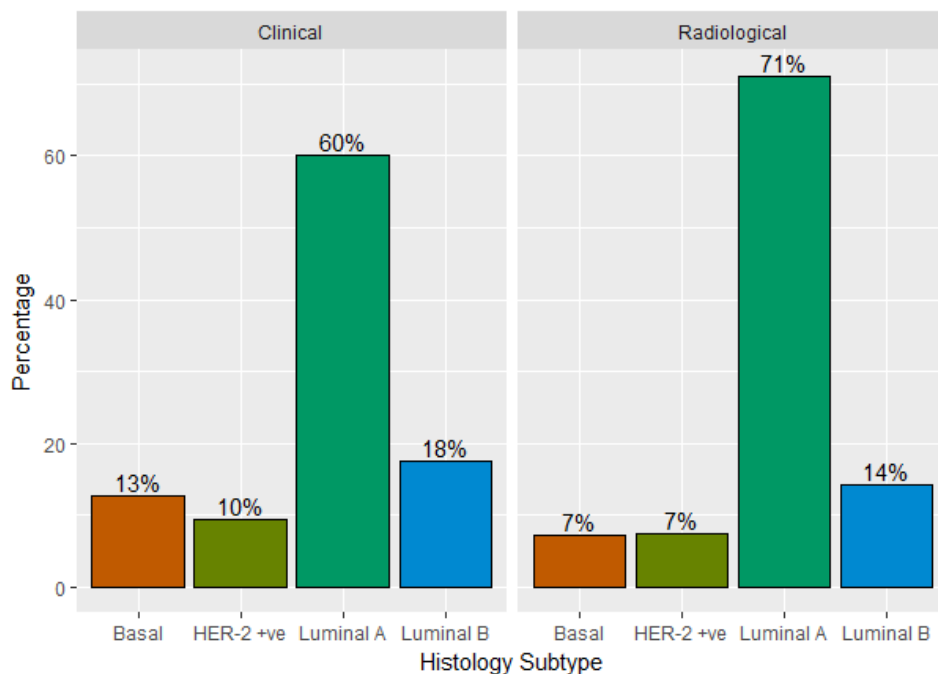


Figure 4-10. Percentage of cases by histology subtype by presentation status.

4.4. Differentiation Grade

Overall, 45% of the tumours were grade 3 (Figure 4-11). Screen detected tumours were of lower grade, with 32% of screen tumours being grade 3 compared to 51% of clinically detectable cancers (Figure 4-12). Among each race, Malays have the highest proportion of grade 3 cancers at 56%, compared to 44% in the Chinese and 45% in the Indians (Figure 4-13).

Table 4-4. Proportion of cases by grade differentiation.

Differentiation	Frequency	Percentage (%)
Grade 1	2,200	14
Grade 2	6,200	40
Grade 3	7,000	45

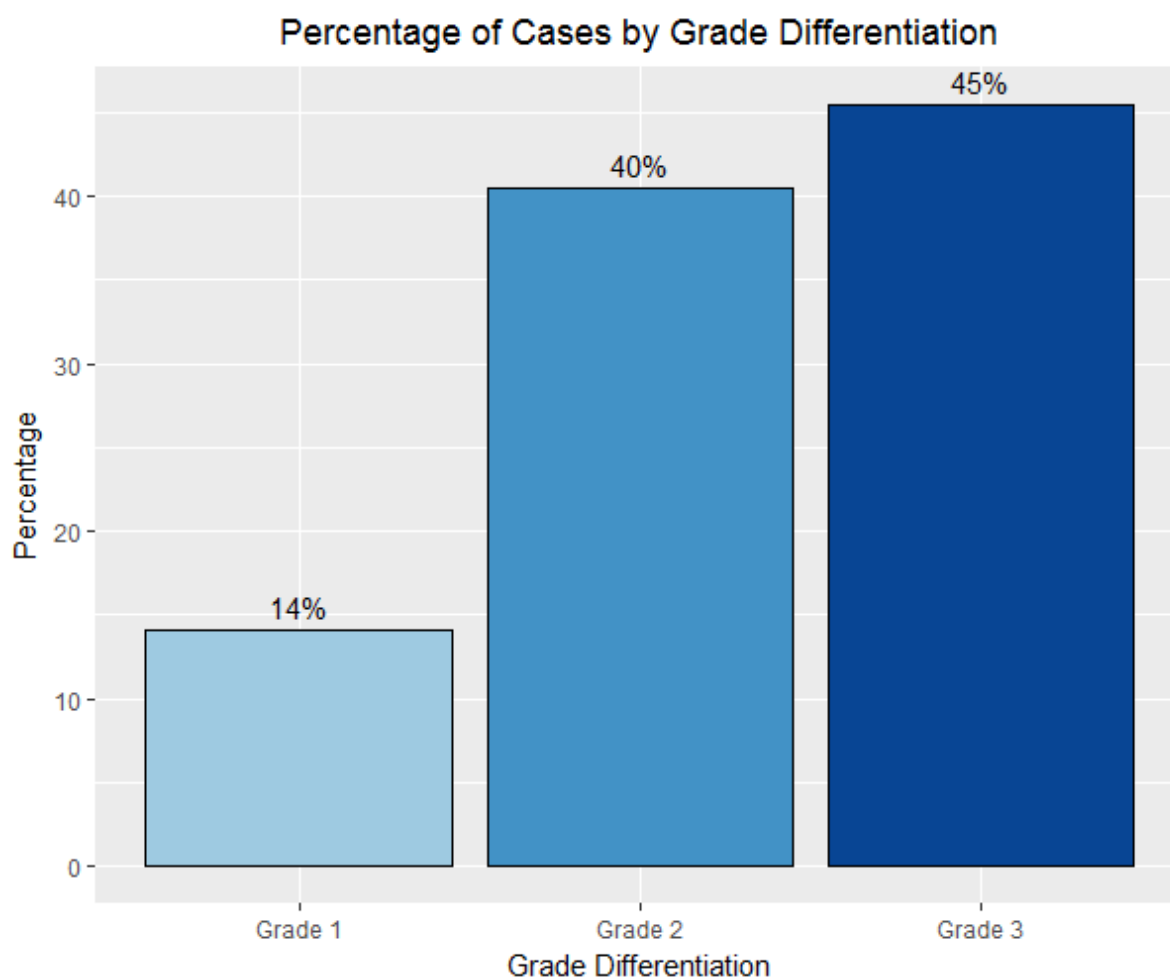


Figure 4-11. Percentage of cases by grade differentiation.

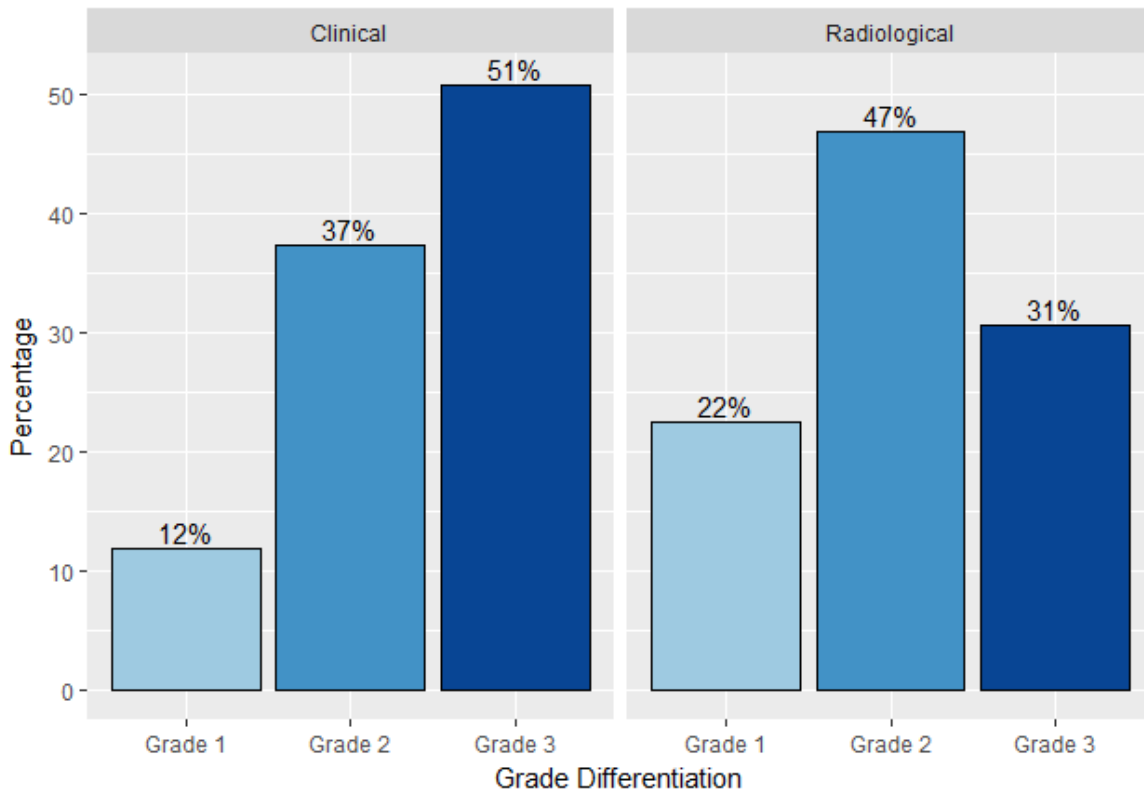


Figure 4-12. Percentage of cases by grade differentiation by presentation type.

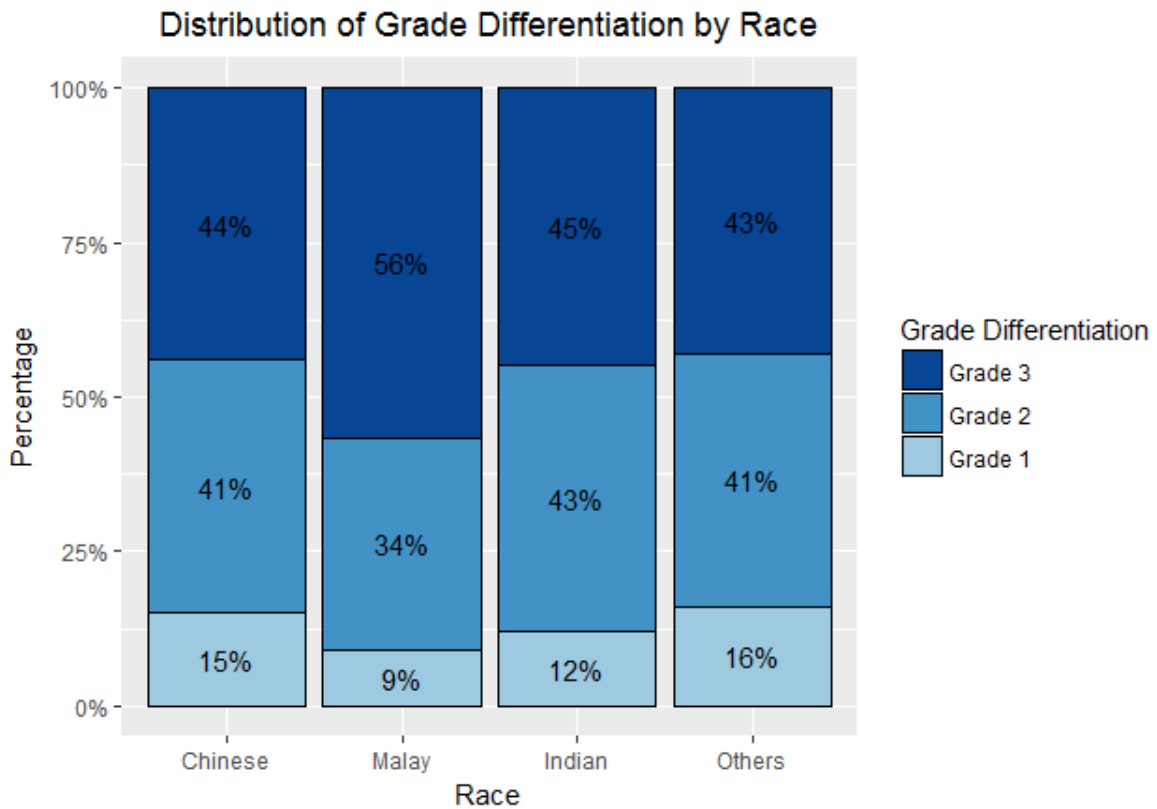


Figure 4-13. Distribution of grade differentiation by race.

4.5. Tumour Size

The mean tumour size at diagnosis for Singapore residents is 2.5cm (IQR 1.3 – 3.2cm) (Table 4-5).

Table 4-5. Summary statistics for tumour size.

Size of cohort	Mean (cm)	SD	Median	1 st Quartile	3 rd Quartile	Minimum (cm)	Maximum (cm)
12,000	2.5	1.7	2.1	1.3	3.2	0	10

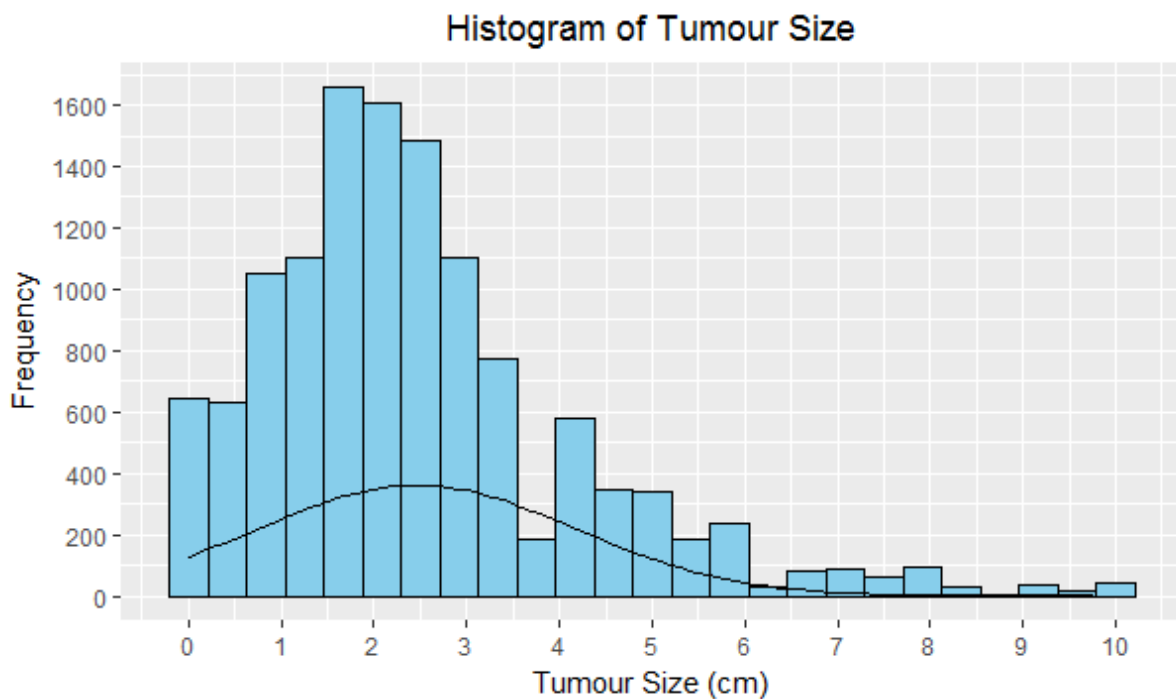


Figure 4-14. Histogram of tumour size.

4.6. Nodal Status

Among the known nodal stage at presentation, N0 dominates the breast cancer cases among the residents in Singapore at about 58% (Figure 4-15). Patients with radiological presentation were more likely to be node negative, 69% compared to 49% of those with clinical presentation (Figure 4-16). Node negative patients were less likely to have received chemotherapy; 49% of node negative patients received chemotherapy, compared to at least 75% in node positive patients (Figure 4-17).

Table 4-6. Percentage of cases by nodal status.

Nodal Stage	Frequency	Percentage
N0	9,000	58
N1	4,200	27
N2	1,400	8.9
N3	920	5.9

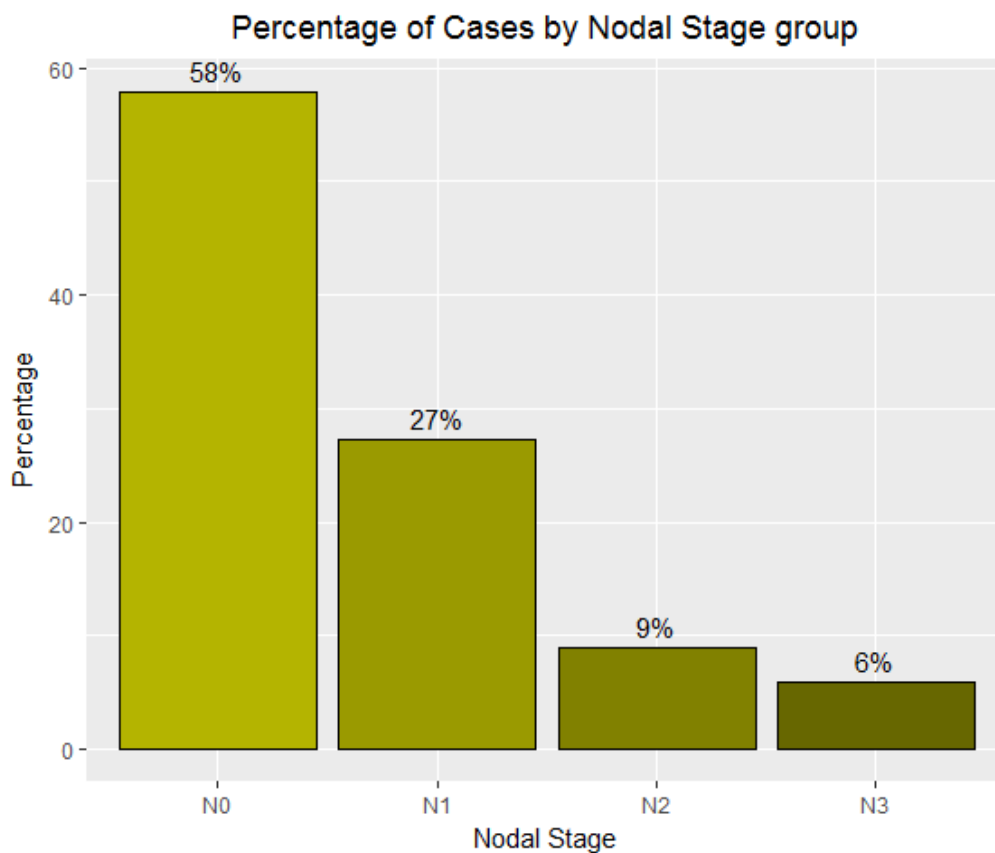


Figure 4-15. Percentage of cases by nodal stage group.

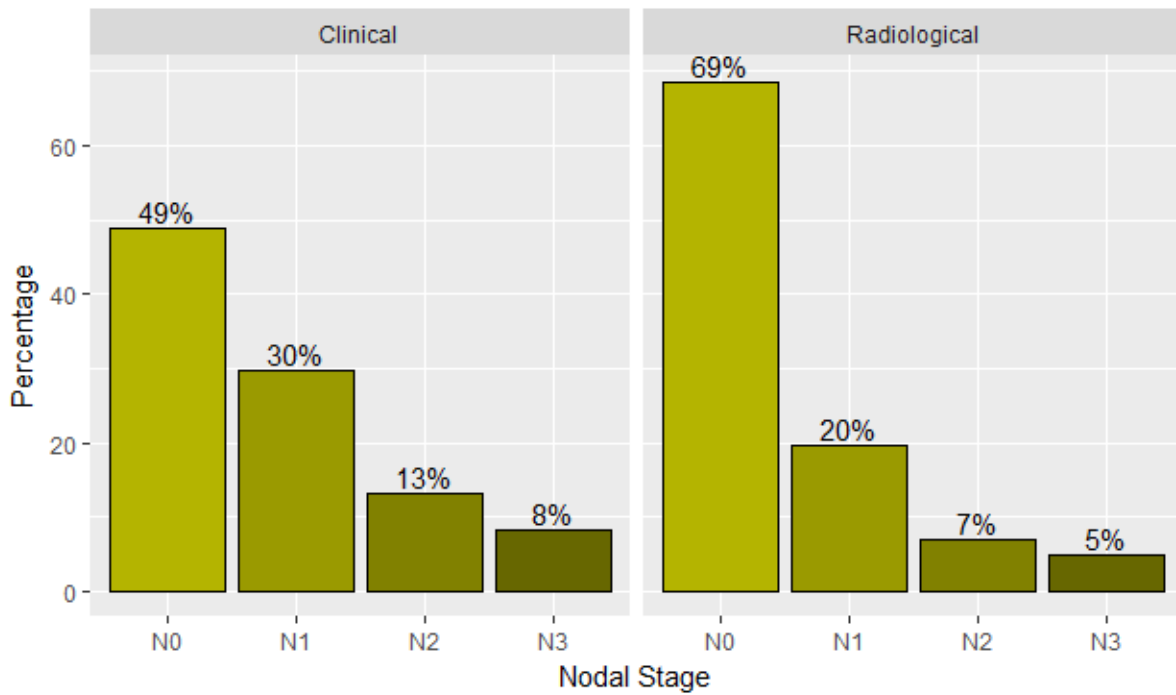


Figure 4-16. Percentage of cases by nodal stage by presentation type.

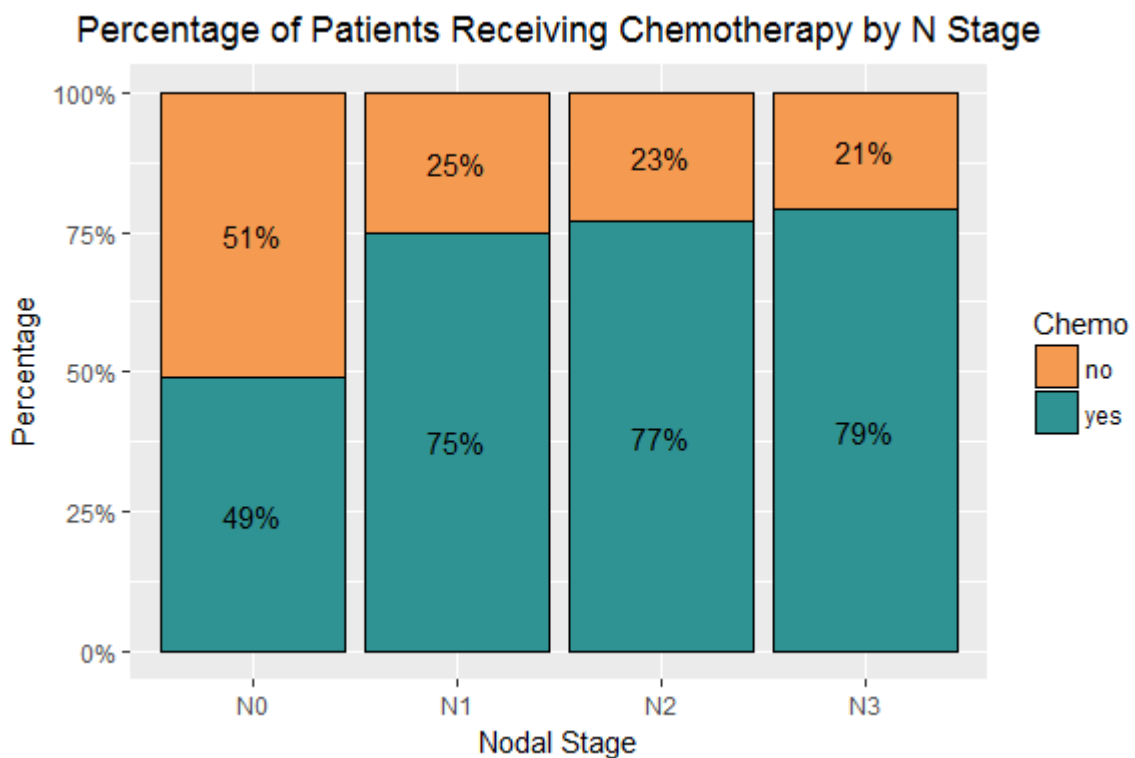


Figure 4-17. Percentage of patients receiving chemotherapy by nodal stage.

5. Treatment

- Among the cohort of breast cancer patients who are Singapore residents, those that are treated with curative intent (i.e. Stages I to III) are analysed -

5.1. Breast Surgery

Among patients where the surgery type is known, 66% had mastectomy (Figure 5-1). Among these patients with mastectomy, 16% of them had undergone reconstruction. The most commonly used reconstruction method is a Transverse Rectus Abdominis Muscle (TRAM) flap. This accounts for 57% of all reconstruction (Figure 5-2).

Table 5-1. Percentage of cases by overall surgery type.

Overall Surgery	Frequency	Percentage (%)
Mastectomy	5,600	56
Breast Conservation Therapy	3,400	34
Mastectomy with Reconstruction	1,000	10
No Surgery	26	0.26

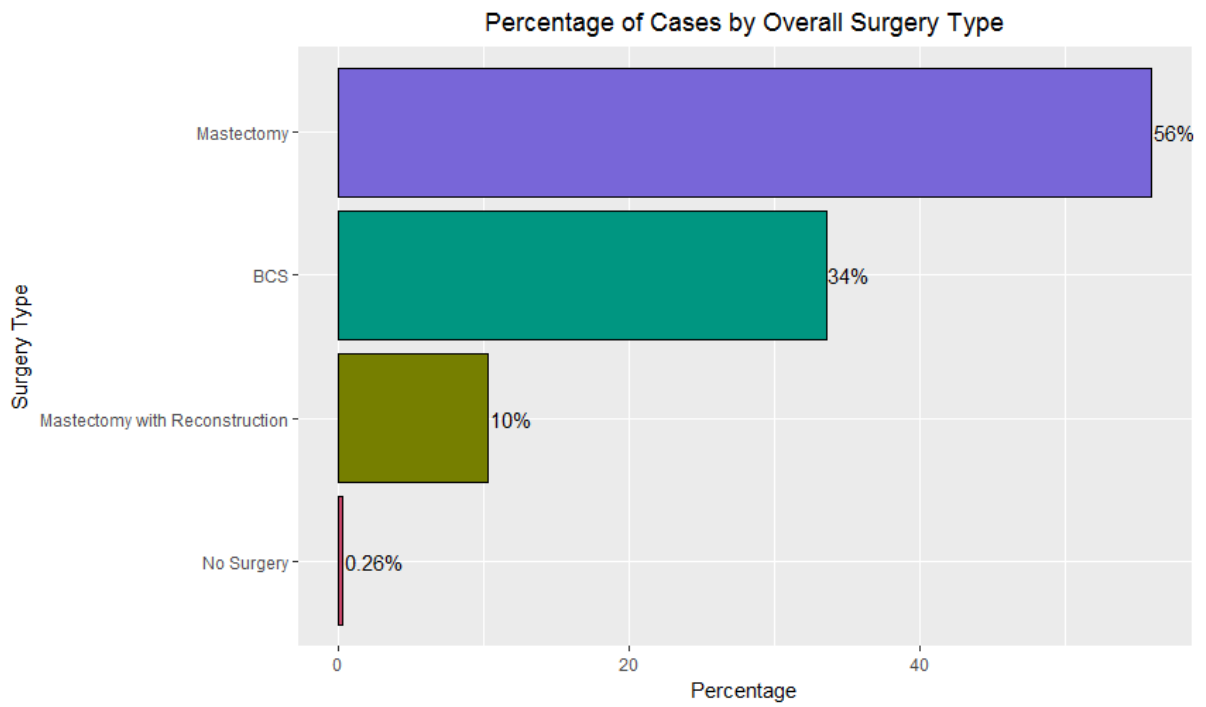


Figure 5-1. Percentage of cases by overall surgery type.

Table 5-2. Percentage of cases by reconstruction type.

Overall Surgery	Frequency	Percentage (%)
TRAM	470	57
LD Flap	140	16
Implants	81	10
Others	150	17

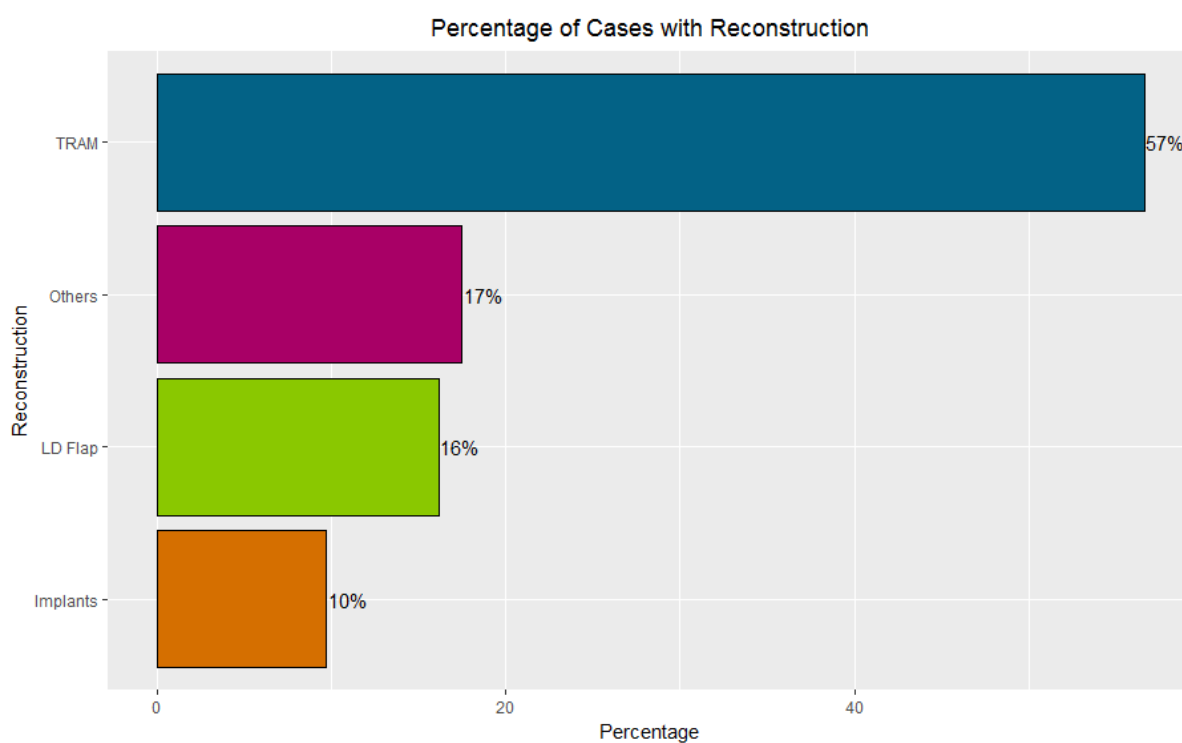


Figure 5-2. Percentage of cases with reconstruction.

The 3 major races in Singapore did not differ with regards to the surgery type (Figure 5-3). Younger subjects were more likely to have had reconstruction (Figure 5-4). In addition, the proportion of breast conservation surgery decreases with increasing age (Figure 5-4) while that for clinical stage increases till stage III (Figure 5-5). In contrast, the proportion of breast reconstruction remains relatively constant at around 10% for tumour sizes less than 5cm, but is higher at 15% for tumour sizes more than 5cm (Figure 5-6). The incidence of reconstruction has risen over the years (Figure 5-7).

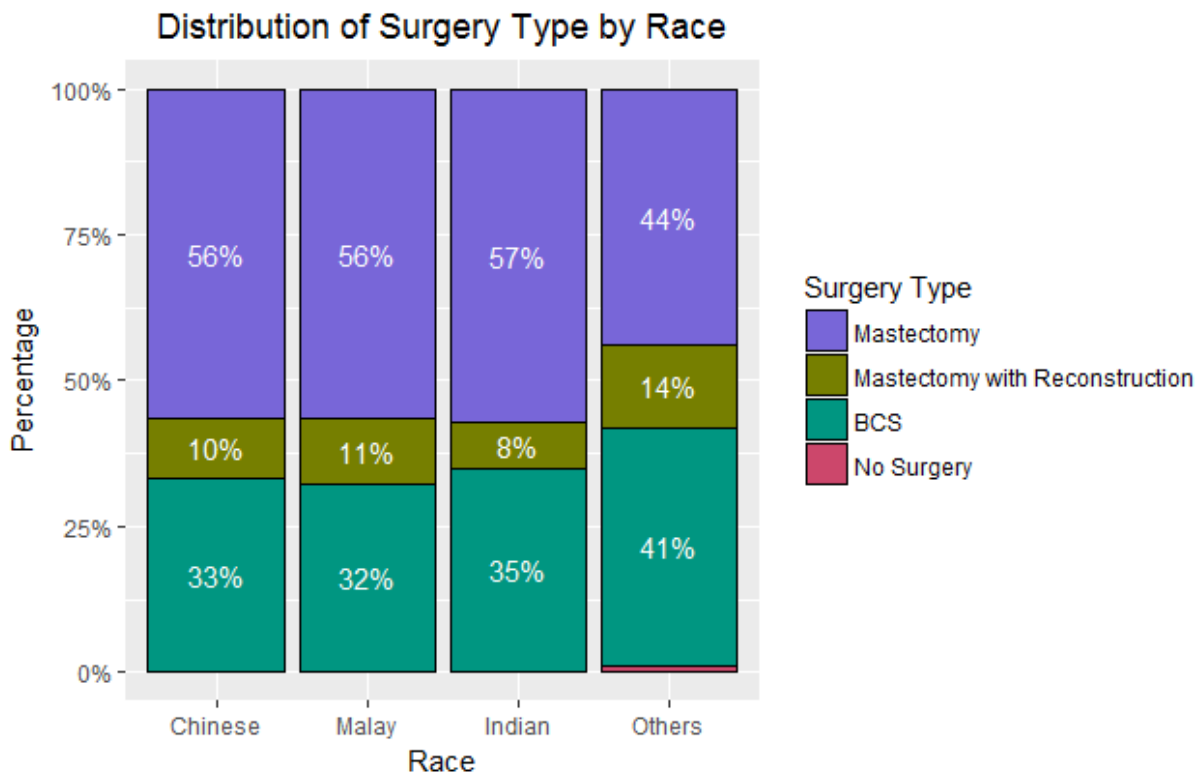


Figure 5-3. Distribution of surgery type by race.

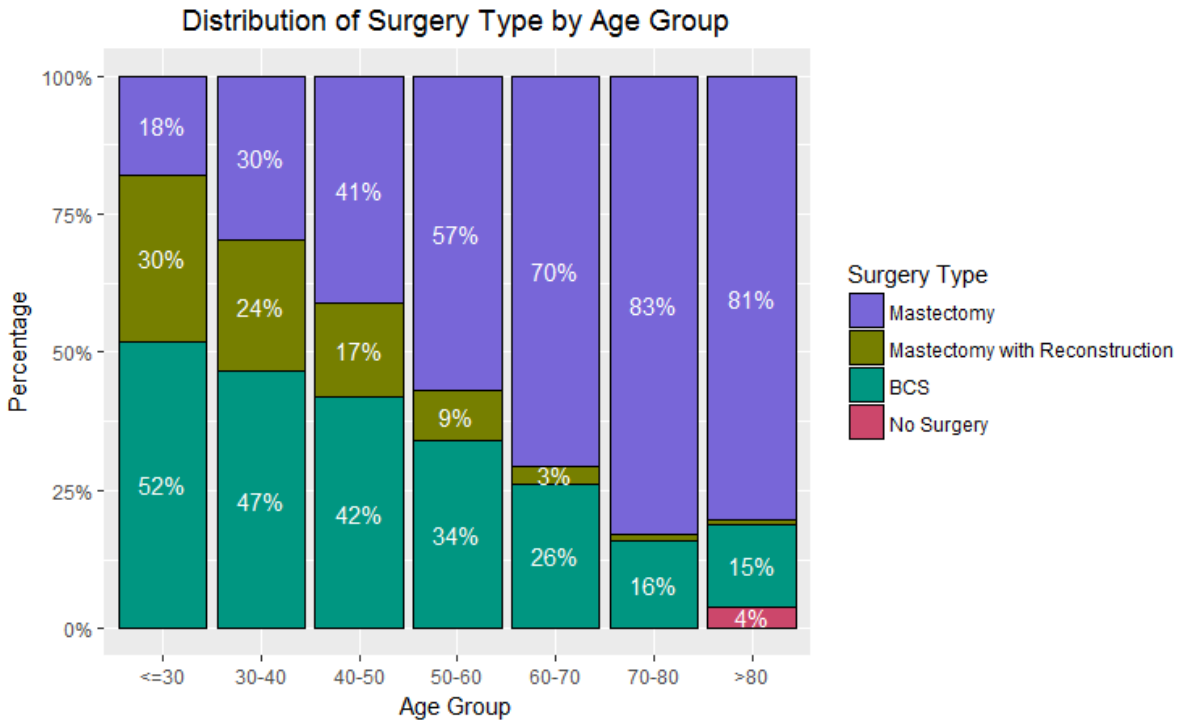


Figure 5-4. Distribution of surgery type by age group.

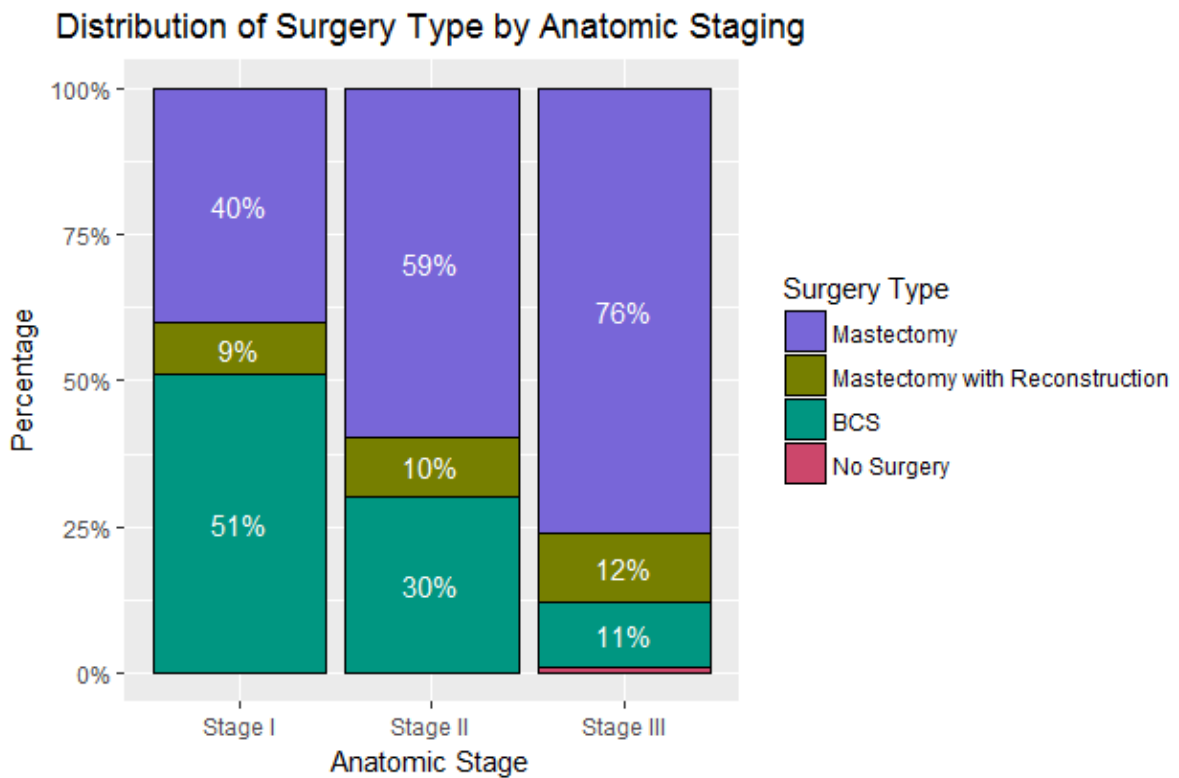


Figure 5-5. Distribution of surgery type by anatomic staging.

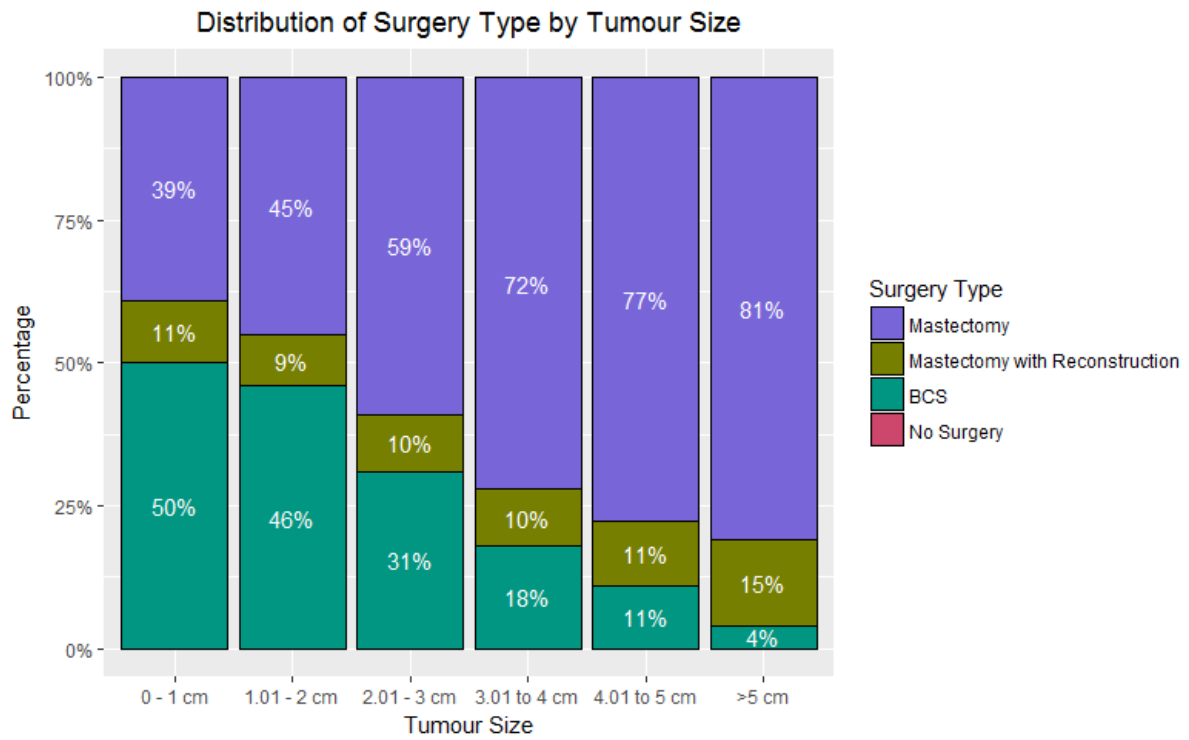


Figure 5-6. Distribution of surgery type by tumour size.

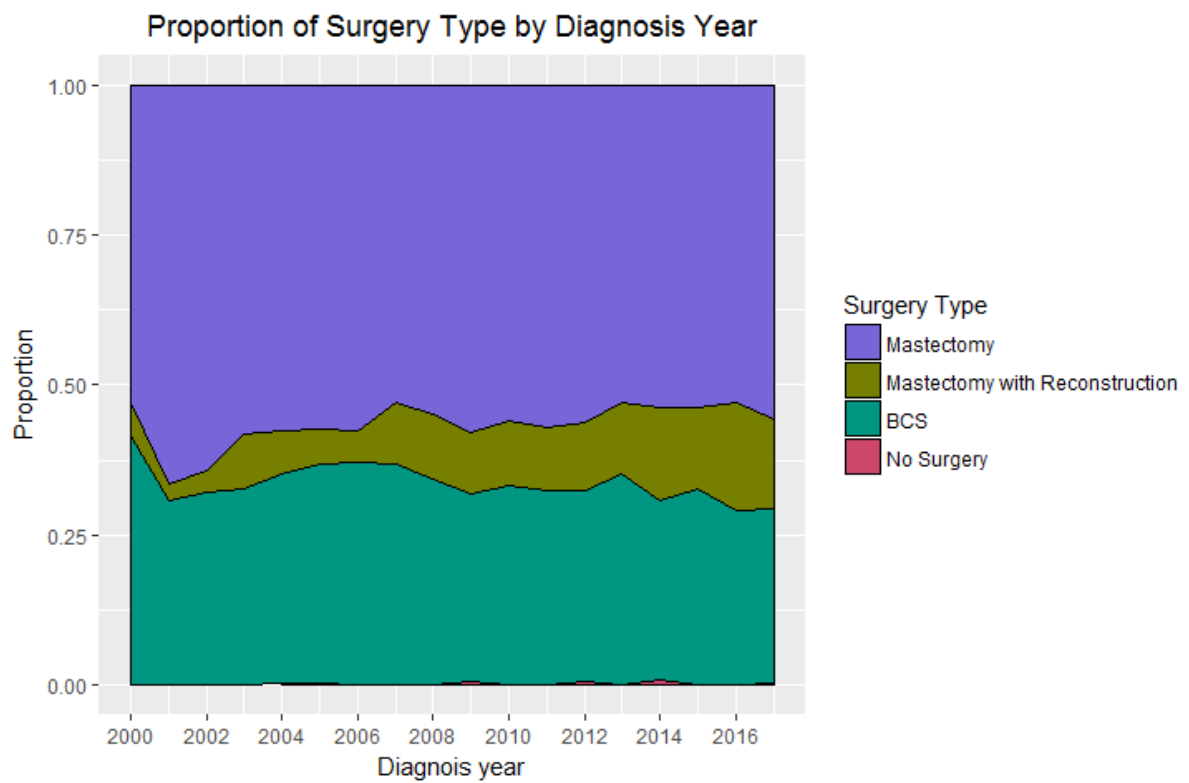


Figure 5-7. Proportion of surgery type by diagnosis year.

5.2. Chemotherapy

63% of patients received chemotherapy as part of initial management (Figure 5-8). Of those who received chemotherapy, almost half of them received both anthracycline and taxane-containing drugs in their treatment (Figure 5-9).

Proportion of Patients who Received Chemotherapy

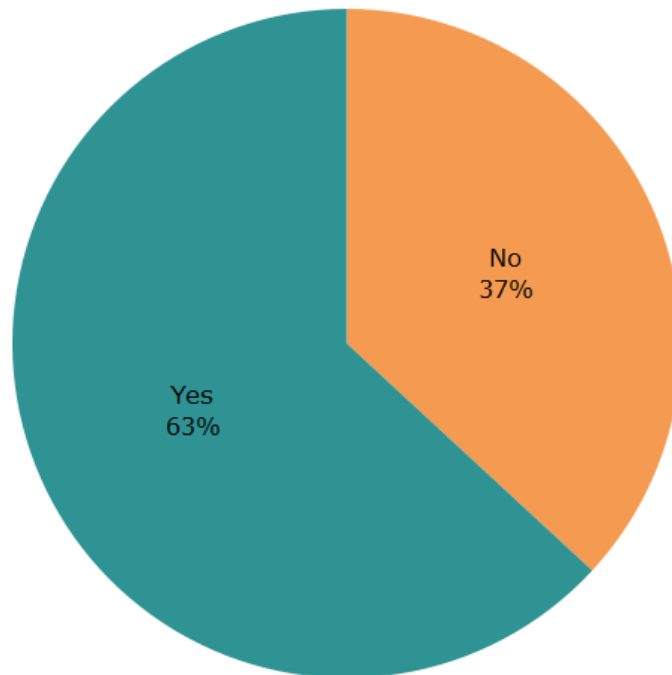


Figure 5-8. Proportion of patients who received chemotherapy.

Distribution of Drugs for Patients who Received Chemotherapy

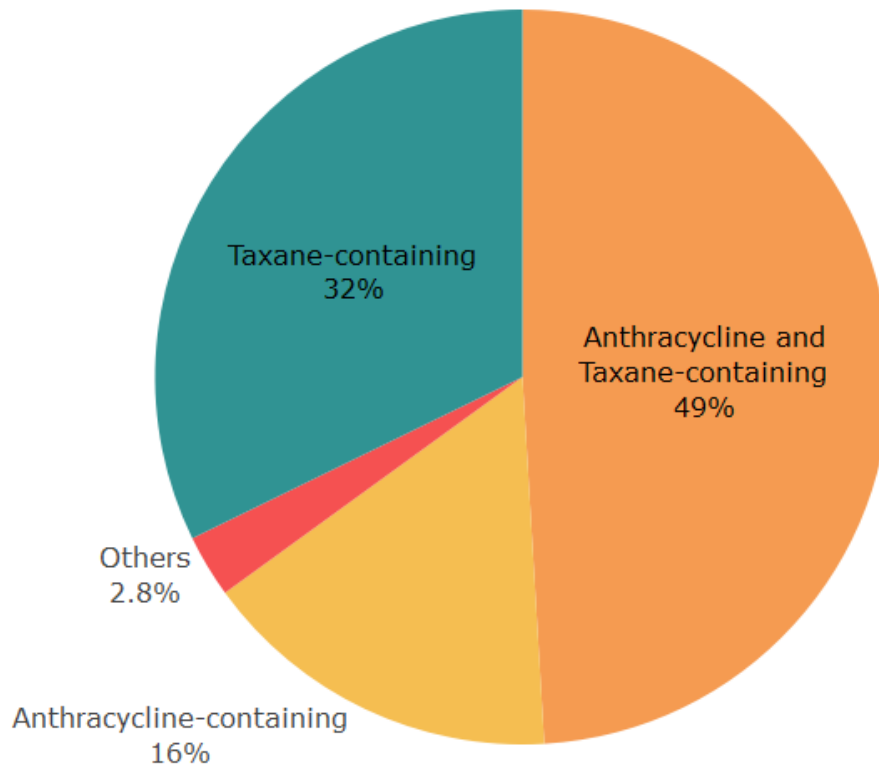


Figure 5-9. Distribution of drugs for patients who received chemotherapy.

Among the 3 major races in Singapore, the proportion of Malays who had received chemotherapy was the highest at 72% (Figure 5-10). The proportion of patients who had received chemotherapy was higher in Stages II and III as compared to Stage I (Figure 5-11).

Percentage of Patients who Received Chemotherapy by Race

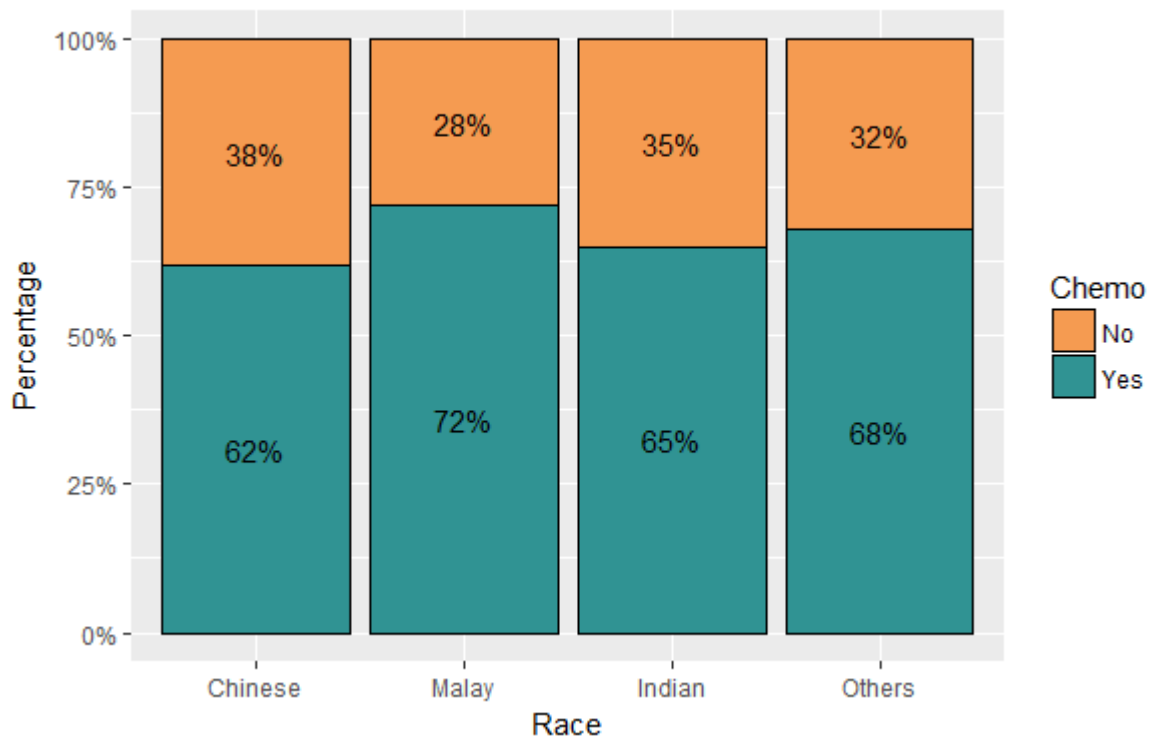


Figure 5-10. Percentage of patients receiving chemo by race.

Percentage of Patients who Received Chemotherapy by Anatomic Stage

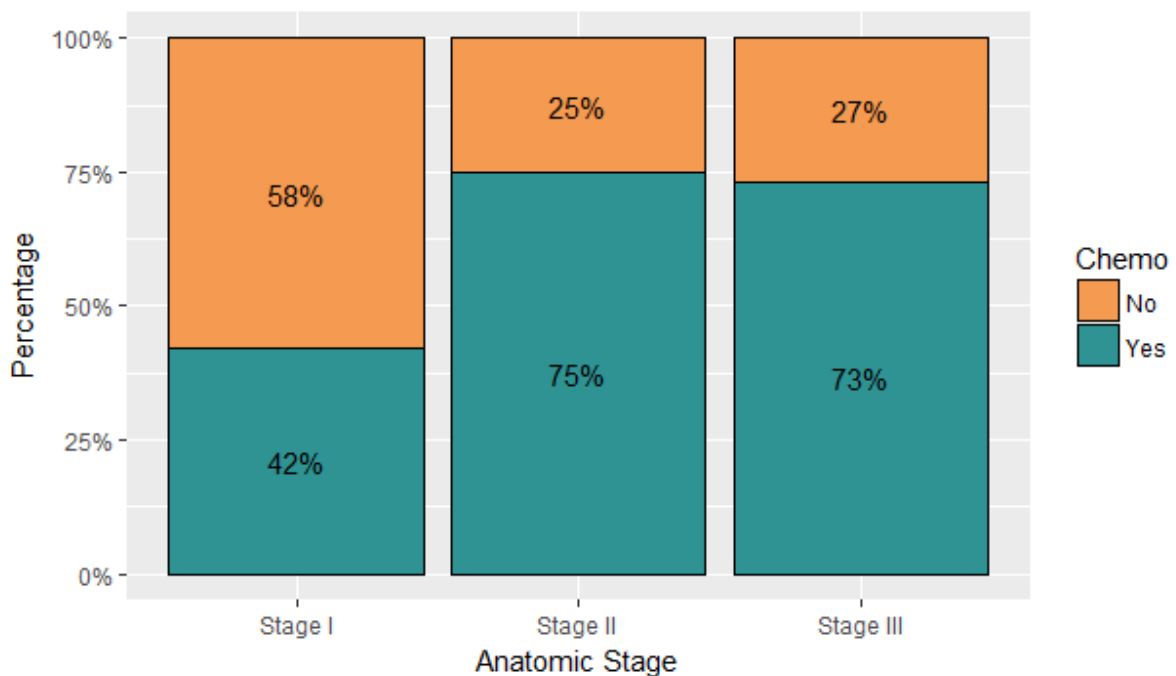


Figure 5-11. Percentage of patients who received chemotherapy by anatomic staging.

Among the 4 histology subtypes of luminal A, luminal B, Her-2 enriched and triple negative breast cancer, patients with luminal A were least likely to have received chemotherapy (56%) (Figure 5-12).

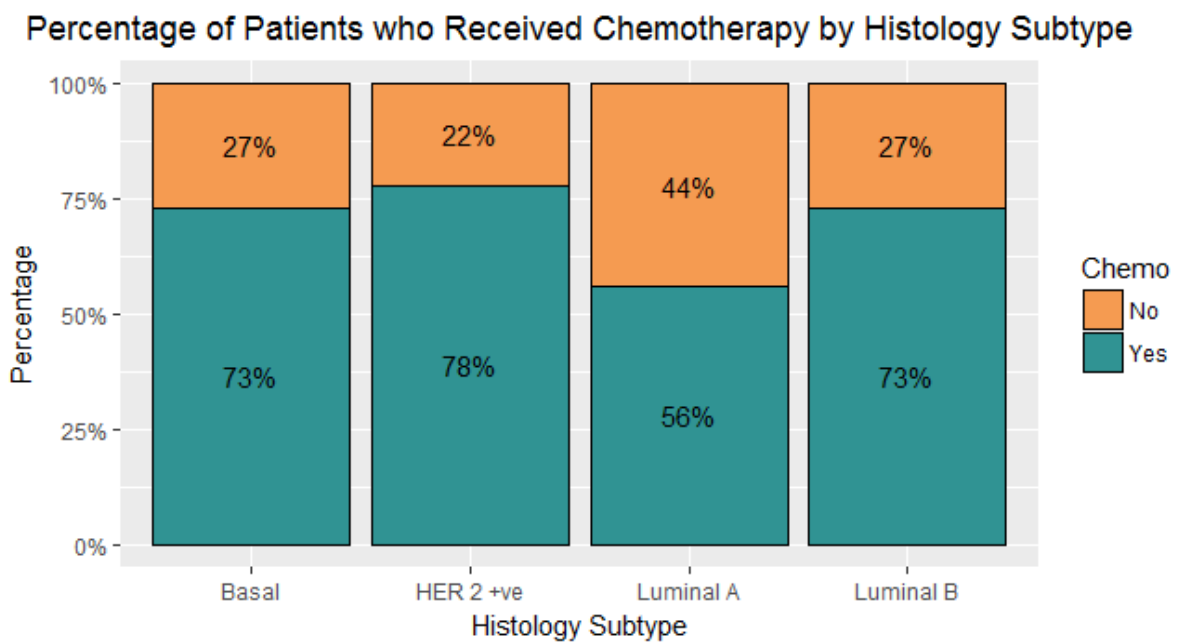


Figure 5-12. Percentage of patients who received chemotherapy by histology subtype.

5.3. Radiation Therapy

This section will mainly be a comparative between mastectomy and breast conservation surgery groups.

Radiotherapy remains the gold standard post breast conservation surgery, barring a few special circumstances for instance the recently published PRIME II trial which showed only a very slightly inferior local outcome in patients older than 65 years old with low risk breast cancer who did not have radiotherapy (Kunkler *et al.*, 2015). Radiotherapy is only indicated post mastectomy in patients with tumours larger than 5cm, or with 4 or more positive nodes. In other circumstances, it is only discussed on a case by cases basis.

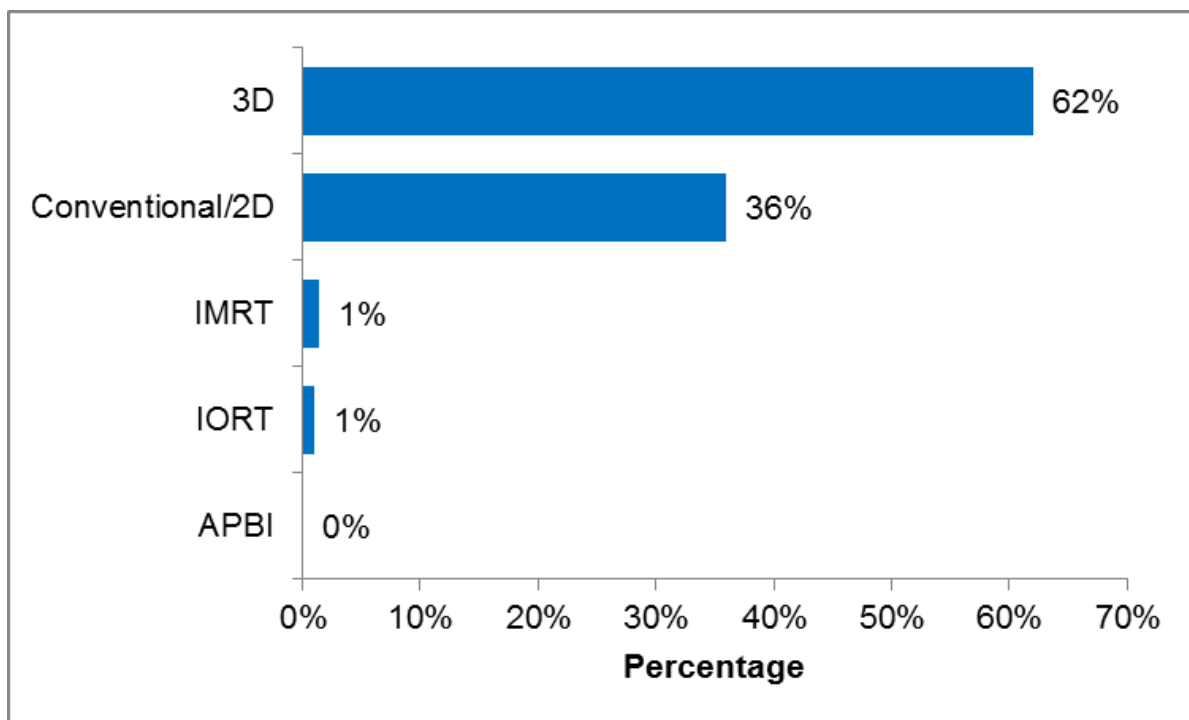


Figure 5-13. Proportion of radiation therapy techniques received by patients.

Opp Tangential fields used to be the main radiotherapy technique used to treat patients. However, there has been a shift towards Plan FD/S and Single Isocentre treatment. Tomotherapy treatment has been picking up around the year 2015 (Figure 5-14).

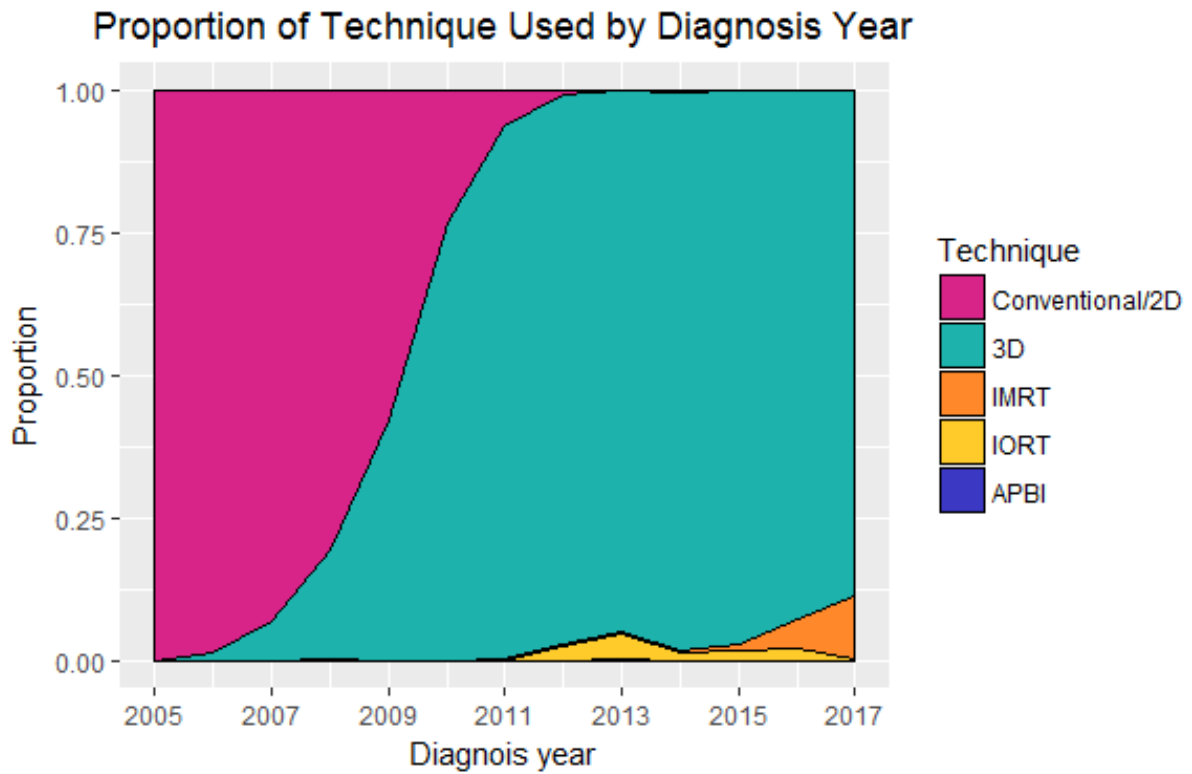


Figure 5-14. Proportion of techniques used by patients by diagnosis year.

Patients used to be treated between 21 to 25 fractions. However the recent years, there is a shift towards treatment between 15 and 20 fractions (Figure 5-15).

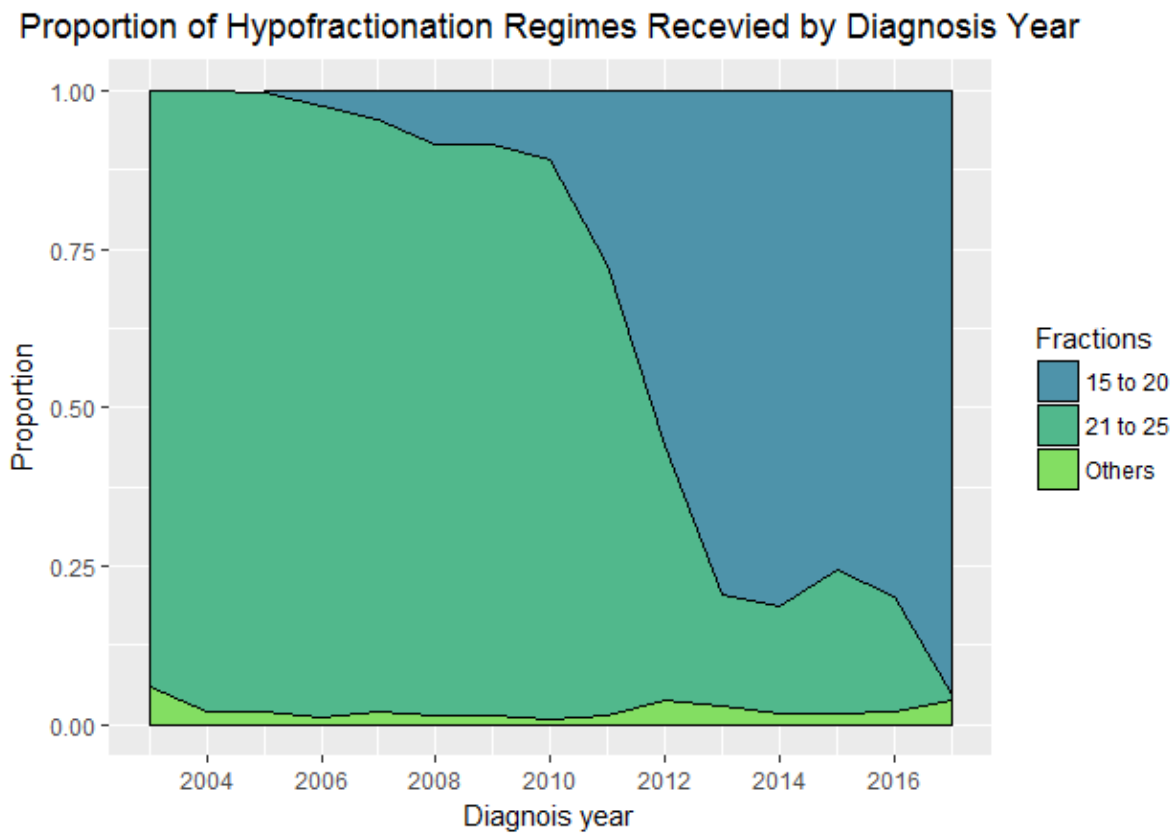


Figure 5-15. Proportion of hypo fractionation regimes received by patients by diagnosis year.

A higher proportion of older patients who had breast conserving surgery did not receive radiotherapy. This trend is reinforced and supported by recent trials such as the PRIME II trial (Kunkler *et al.*, 2015). A higher proportion of older patients with mastectomy also did not receive radiotherapy. This trend is likely due to older patients preferring mastectomy over breast conservation surgery when comparing stage for stage with younger patients.

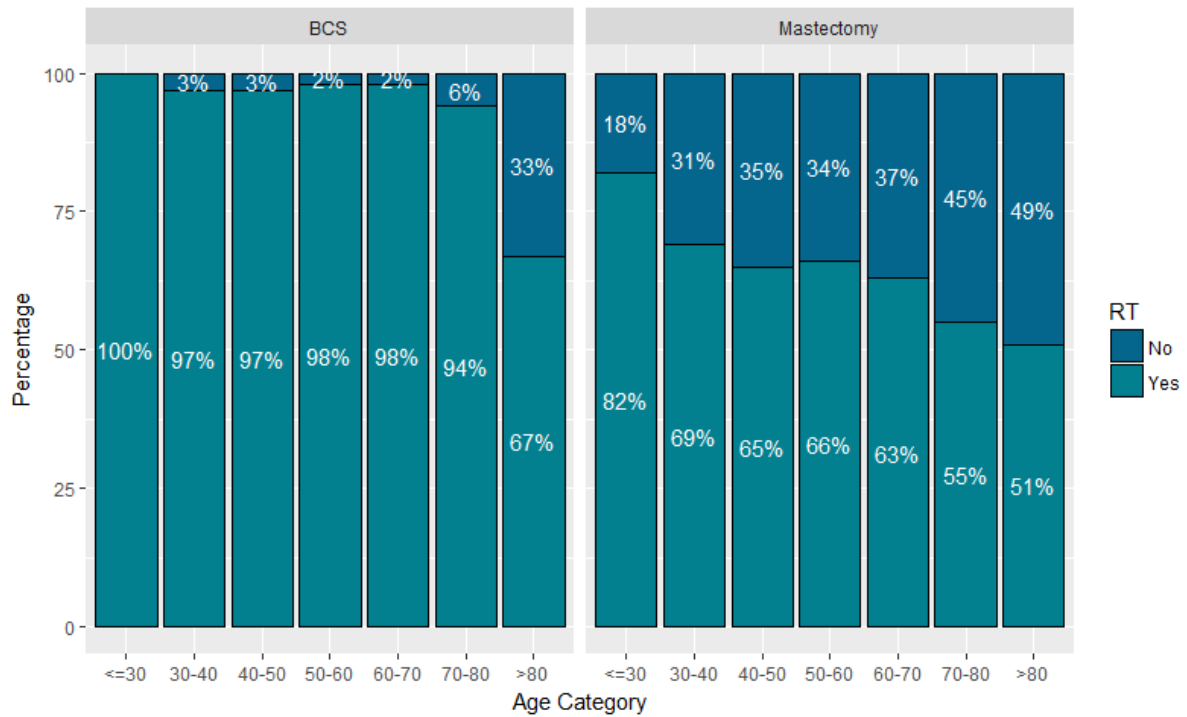


Figure 5-16. Proportion of patients receiving radiation therapy by surgery type and age group.

Among those with mastectomy, 13% of stage I, 57% of stage II and 93% of stage III patients received radiation therapy (Figure 5-17). This is in line with prevailing guidelines recommending adjuvant radiation for higher risks patients.

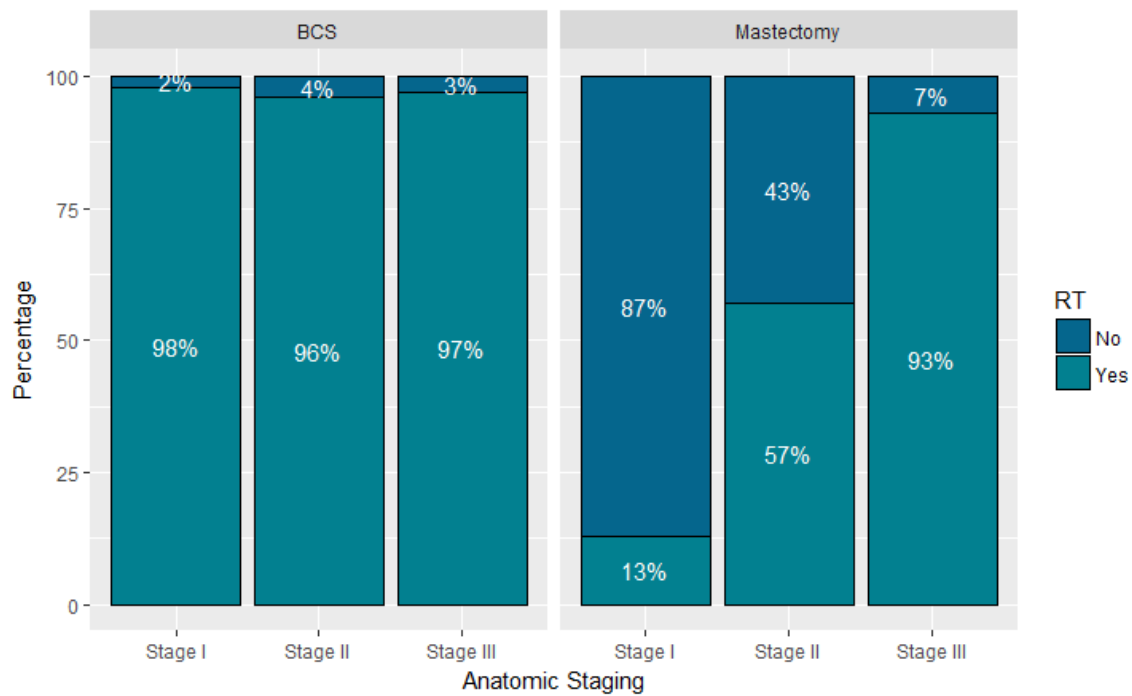


Figure 5-17. Proportion of patients receiving radiation therapy by surgery type and anatomic stage group.

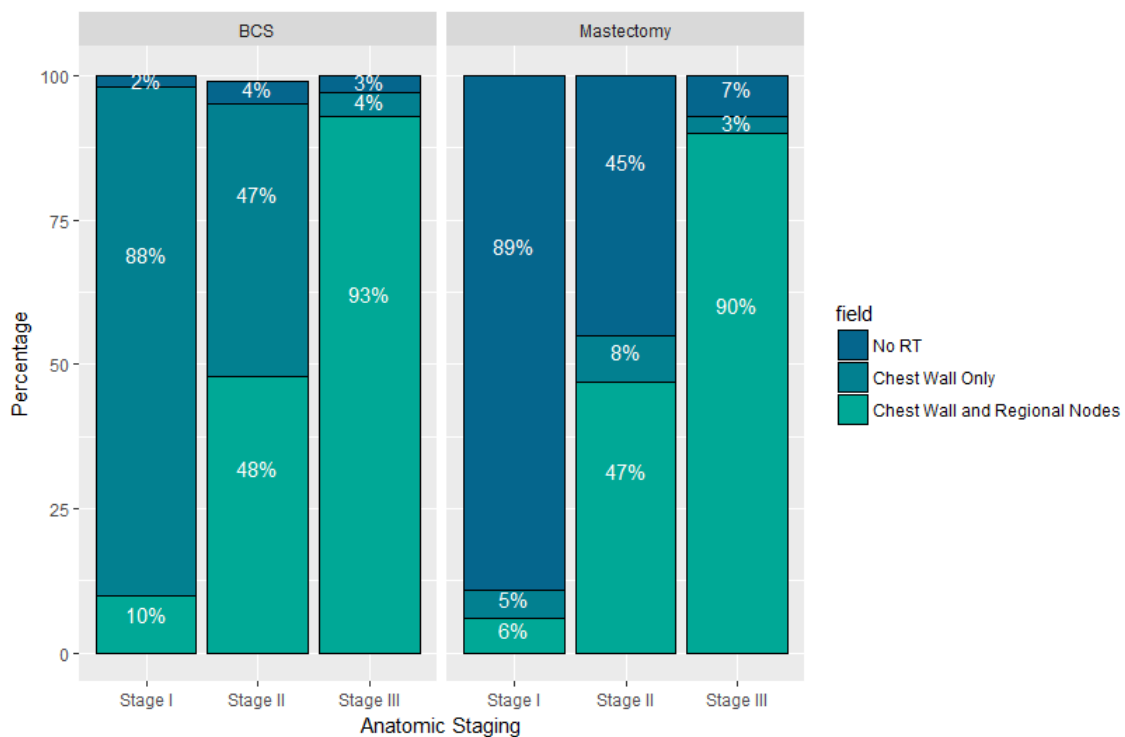


Figure 5-18. Distribution of radiation therapy field that patients received by surgery type and anatomic stage group.

5.4. Targeted Treatment

Increasingly, more patients had received targeted treatment, with a sharp rise in 2014 (Figure 5-19). Most patients will have received targeted treatment in recent years should they be diagnosed with HER2 positive and have undergone chemotherapy (Figure 5-20).

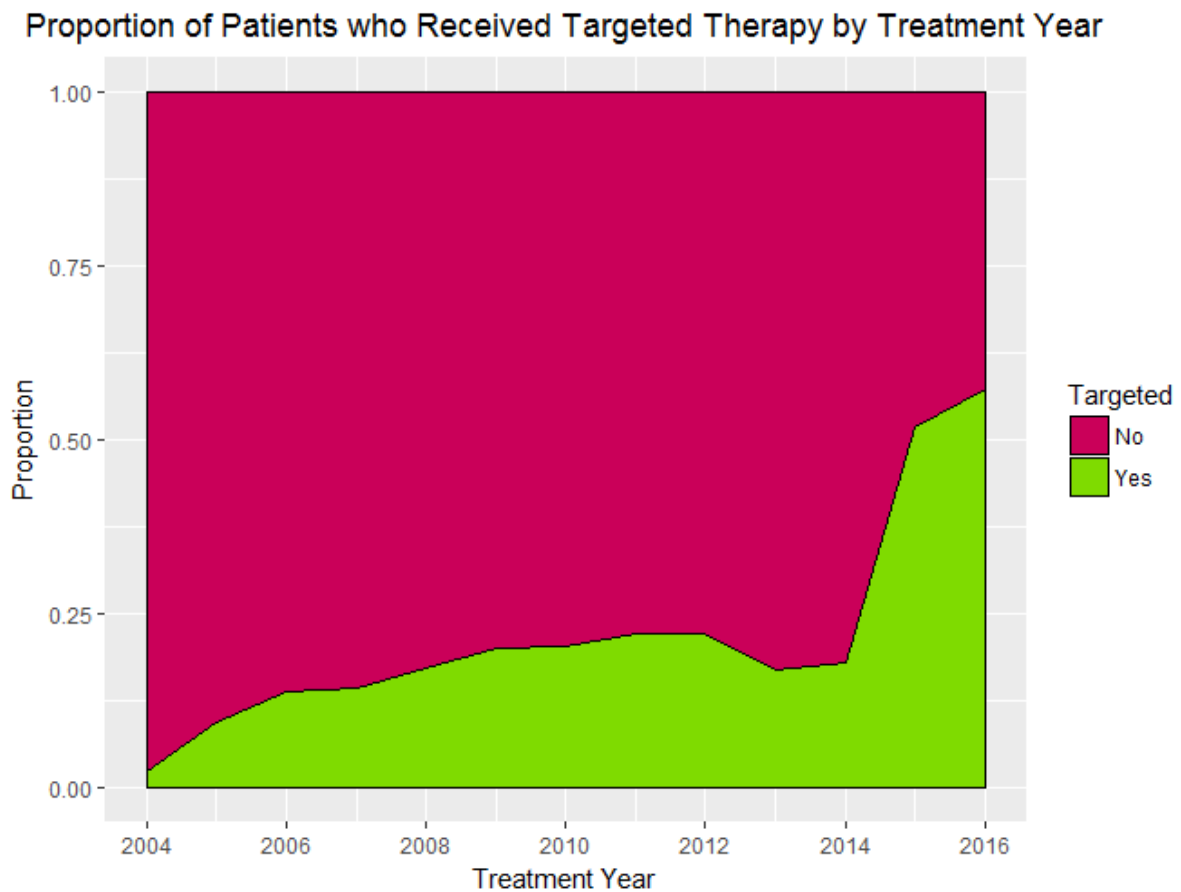


Figure 5-19. Proportion of patients who received targeted treatment by treatment year.

Use of Targeted Therapy in Patients who are HER2 Positive and had Chemotherapy by Treatment Year

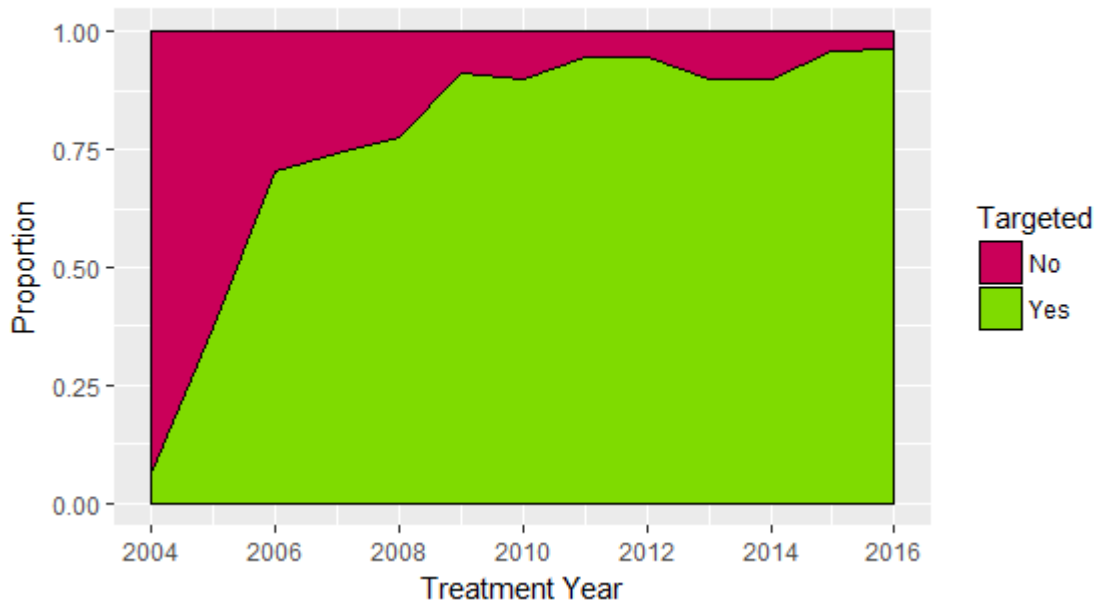


Figure 5-20. Use of targeted therapy in patients who are HER2 positive and had chemotherapy by treatment year.

Targeted Therapy Uptake in Patients who are Node Positive or had Chemotherapy by Treatment Year

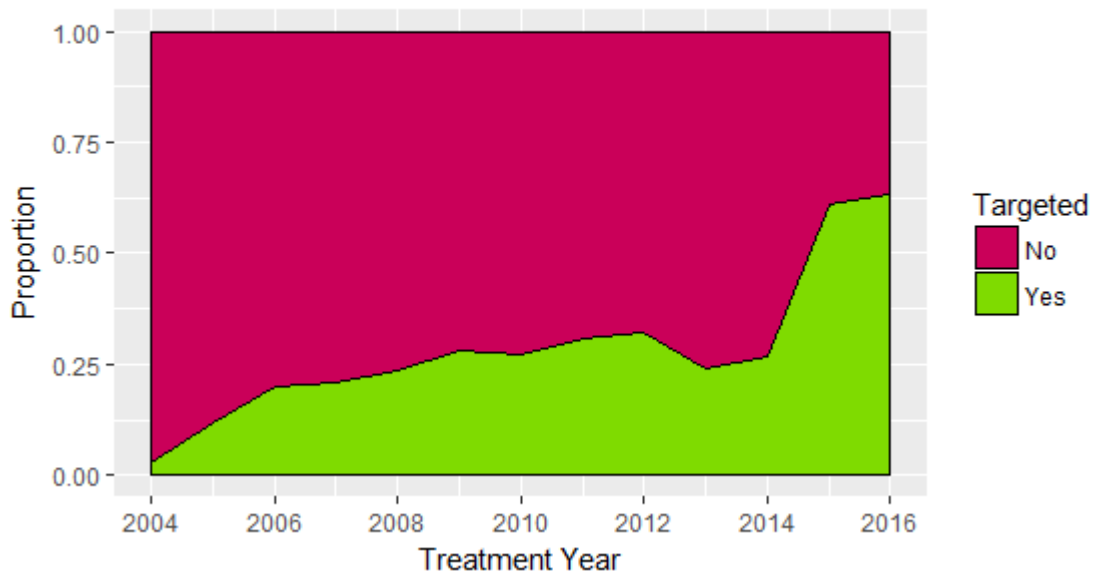


Figure 5-21. Uptake of targeted therapy in patients who are node positive or had chemotherapy by treatment year.

The proportion of patients who had received targeted treatment increased with stage (Figure 5-22).

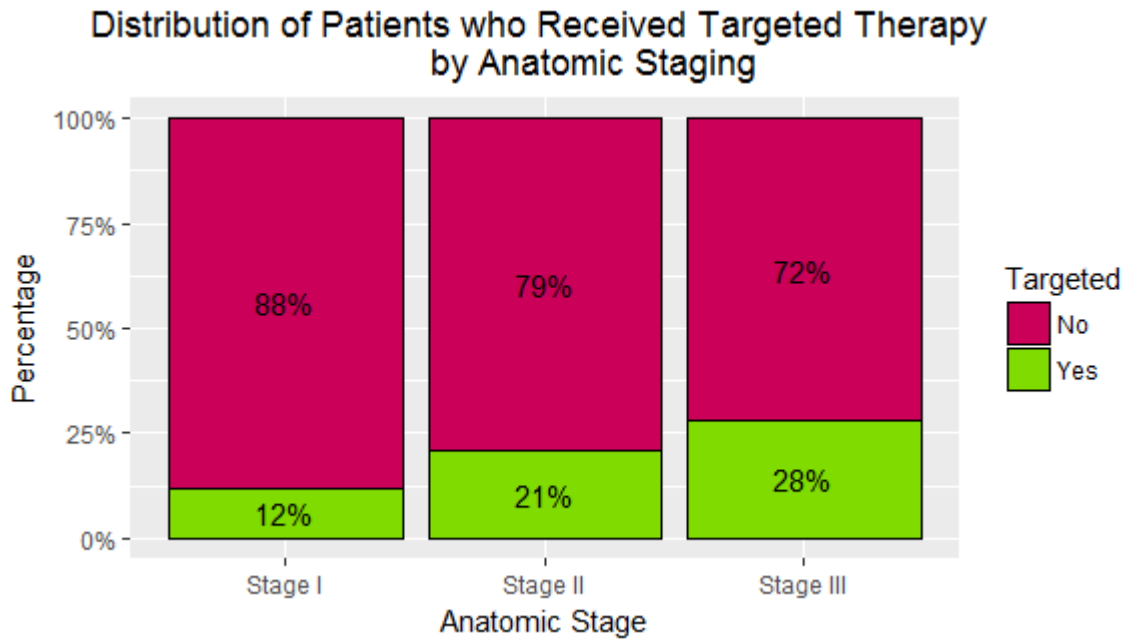


Figure 5-22. Distribution of patients who received targeted therapy by anatomic staging.

5.5. Neo-Adjuvant Chemotherapy Treatment

Neoadjuvant chemotherapy has been used with increasing frequency in recent years (Figure 5-23).

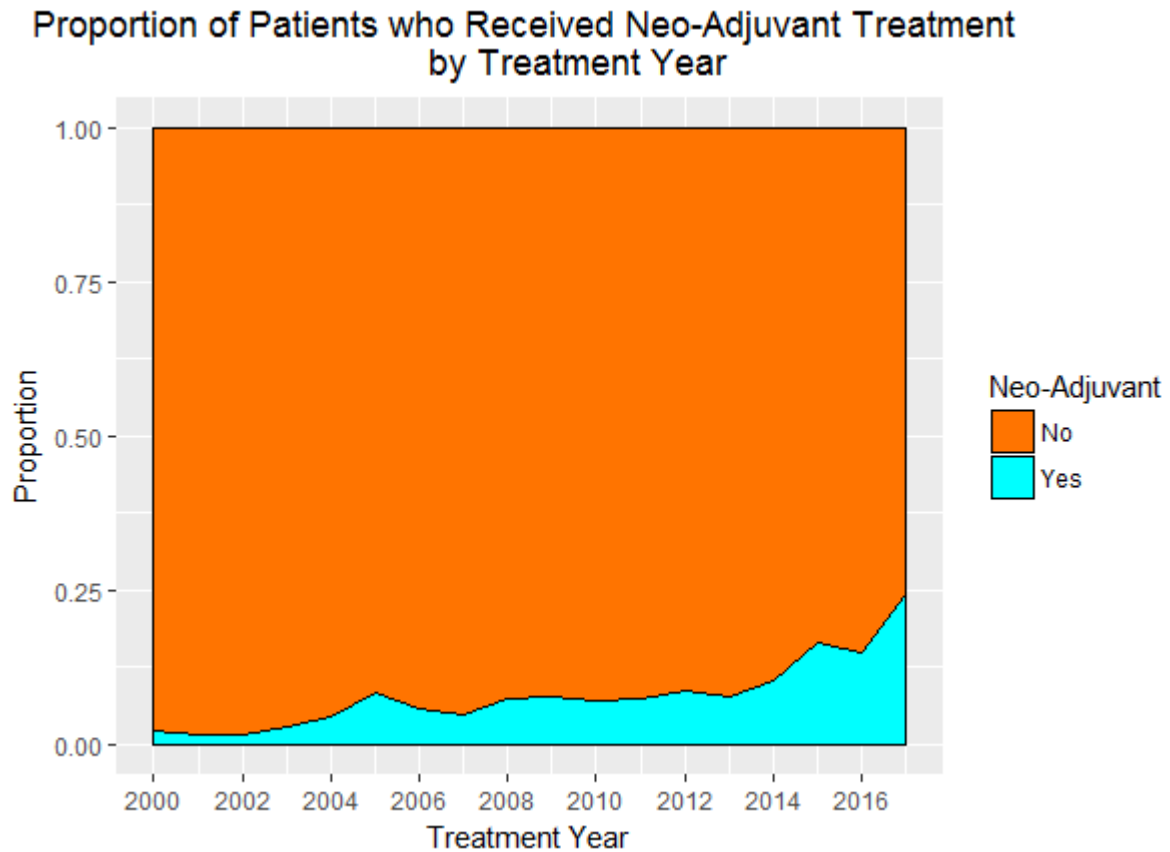


Figure 5-23. Proportion of patients who received neo-adjuvant treatment by treatment year.

6. Survival and Outcomes

In the following sections, we report the outcomes of patients in the cohort of Singapore residents with respect to Overall Survival (OS), Disease Free Survival (DFS), Ipsilateral Breast Tumour Recurrence (IBTR) and Distant Disease Free Survival (DDFS).

The survival time for the respective outcomes are defined by the time difference between the date of diagnosis of primary breast cancer and the corresponding survival end point described in Table 6-1. If the patient did not experience the outcome, the last seen date of the patient will be the survival end point.

Table 6-1. Definition of the survival end points.

Survival	Survival End Point
OS	Death from any cause
DFS	First occurrence of any recurrence arising from primary breast cancer
IBTR	First local recurrence arising from primary breast cancer
DDFS	First distant failure arising from primary breast cancer



We have created an online calculator based on the JBCR cohort. This calculator performs real-time survival analysis by the Kaplan Meier method of a cohort of patients that can be defined by age, tumour staging, nodal staging, metastasis status, hormone receptor status and HER-2 status. Some snapshots of the online survival calculator are shown in Figure 6-1.

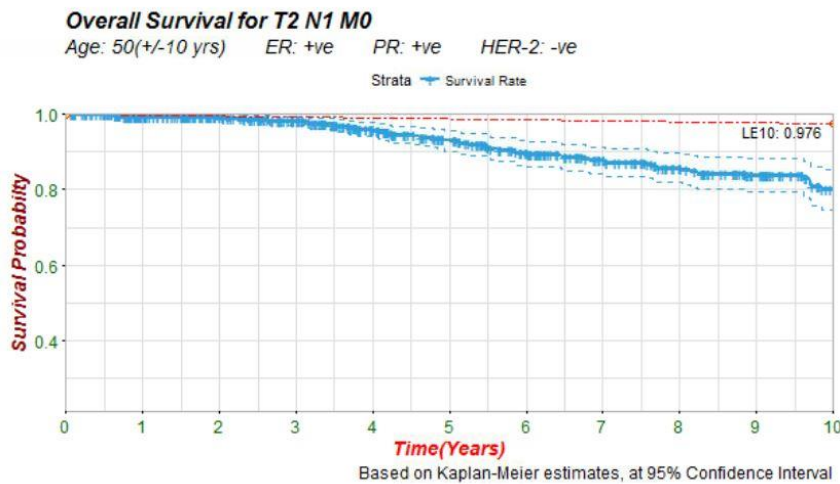
T Stage Estrogen Receptor status (ER)
 N Stage Progesterone Receptor Status (PR)
 M Stage HER-2 status (HER-2) Age (optional)

(a)

Survival Estimates for T2 N1 M0 - Breast



This graph is an estimation of survival rates up to 10 years after diagnosis. Results are based on selected inputs.



(b)

5-Year Estimate



In a group of 100 patients with the same characteristics as selected, **89 to 95** of them are likely to be alive 5 years from their diagnosis.

These estimates are based on the real world outcome of patients treated in our institutions. Your exact experience may differ within the limits of this prediction. Survival estimates can be unreliable the further into the future prediction is made as there are less patients to base this estimate on

(c)

Figure 6-1. Snapshots of the online survival calculator. (a) Selection Criteria for outcomes estimation. (b) Survival curve of matched population. (c) Icon array for easy visual interpretation of outcomes.

6.1. Overall Survival

Overall, among the 3 major races in Singapore, Malays had the lowest overall survival (Figure 6-2). As expected, the survival curves separate out distinctly according to stage (Figure 6-3). Subjects with luminal A subtype have the best survival outcomes, followed by luminal B, Her-2 enriched then triple negative (Figure 6-4). However, the difference becomes less marked after 10 years. The overall survival curves also separated out according to T (Figure 6-5) and N (Figure 6-6) stages, as well as the grade of differentiation (Figure 6-7).

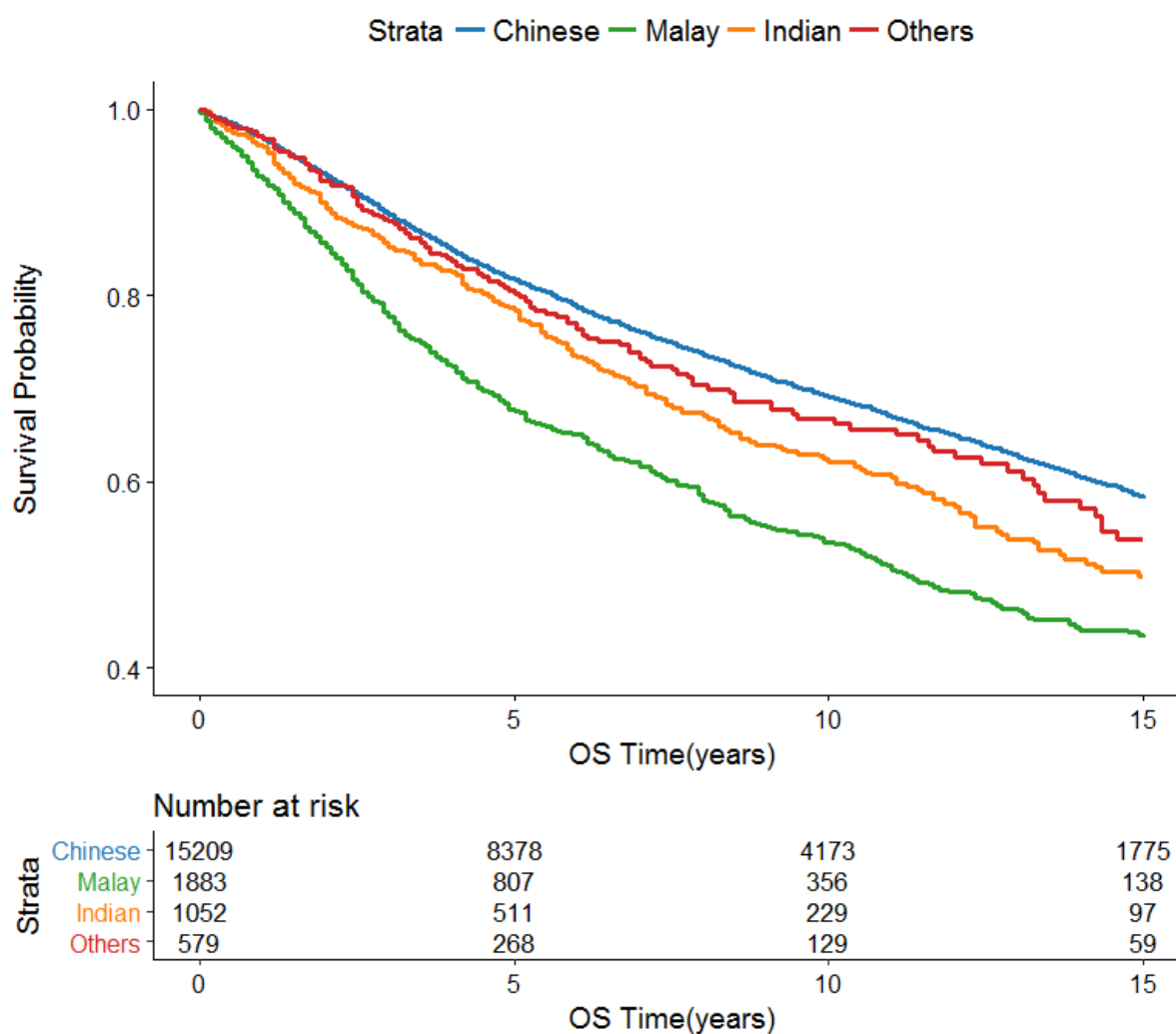


Figure 6-2. Overall survival by race.

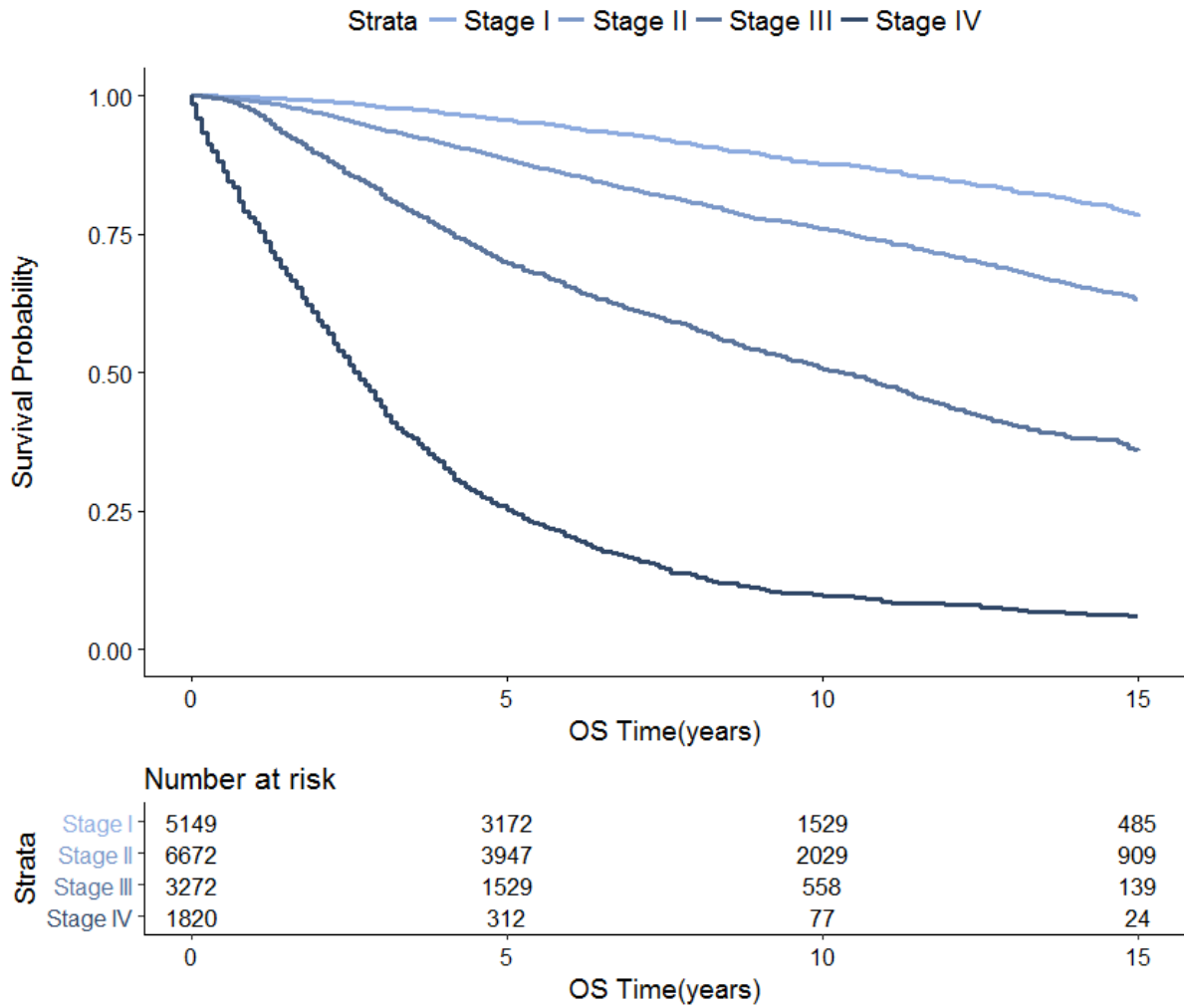


Figure 6-3. Overall survival by anatomic stage group.

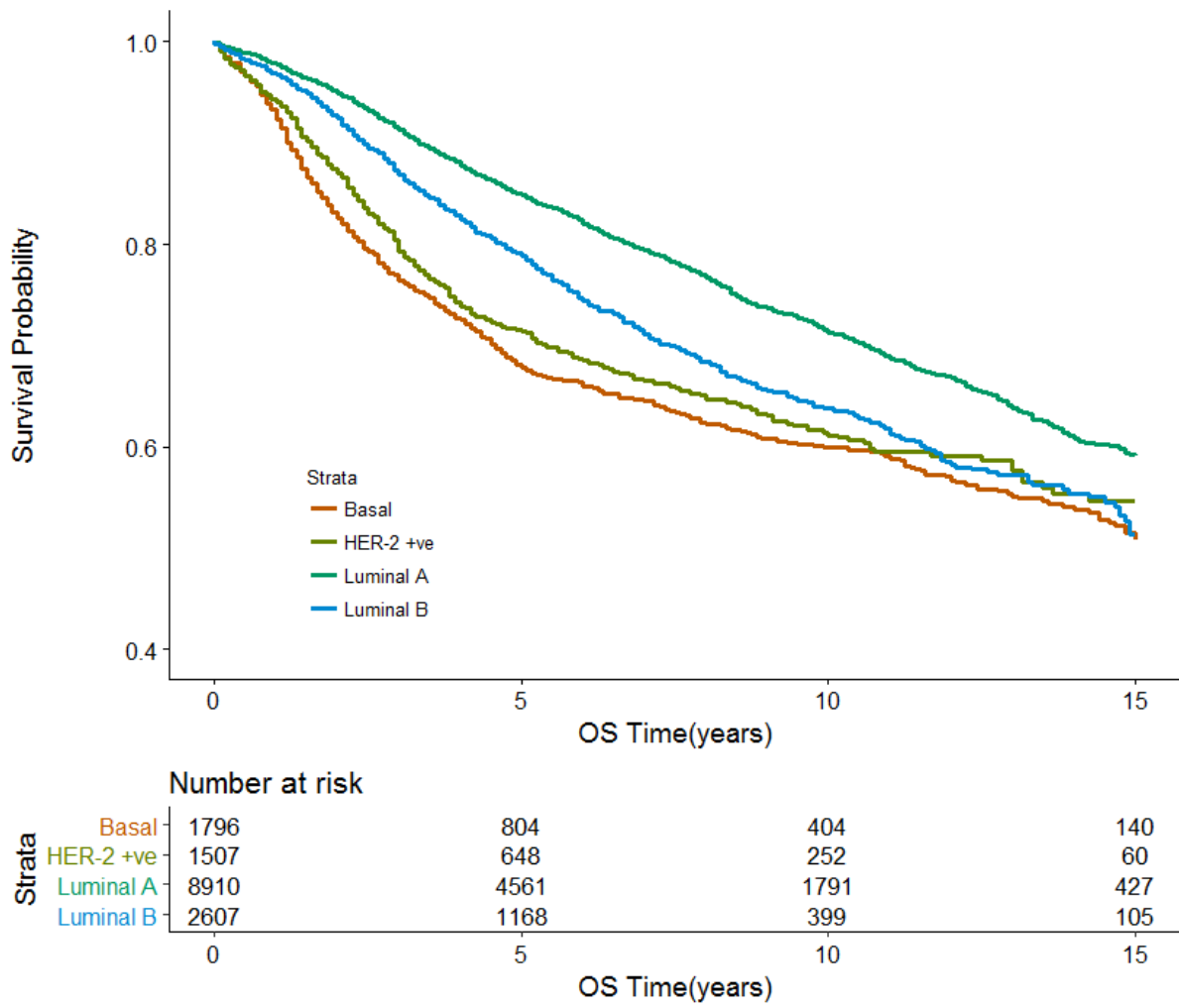


Figure 6-4. Overall survival by histology subtype.

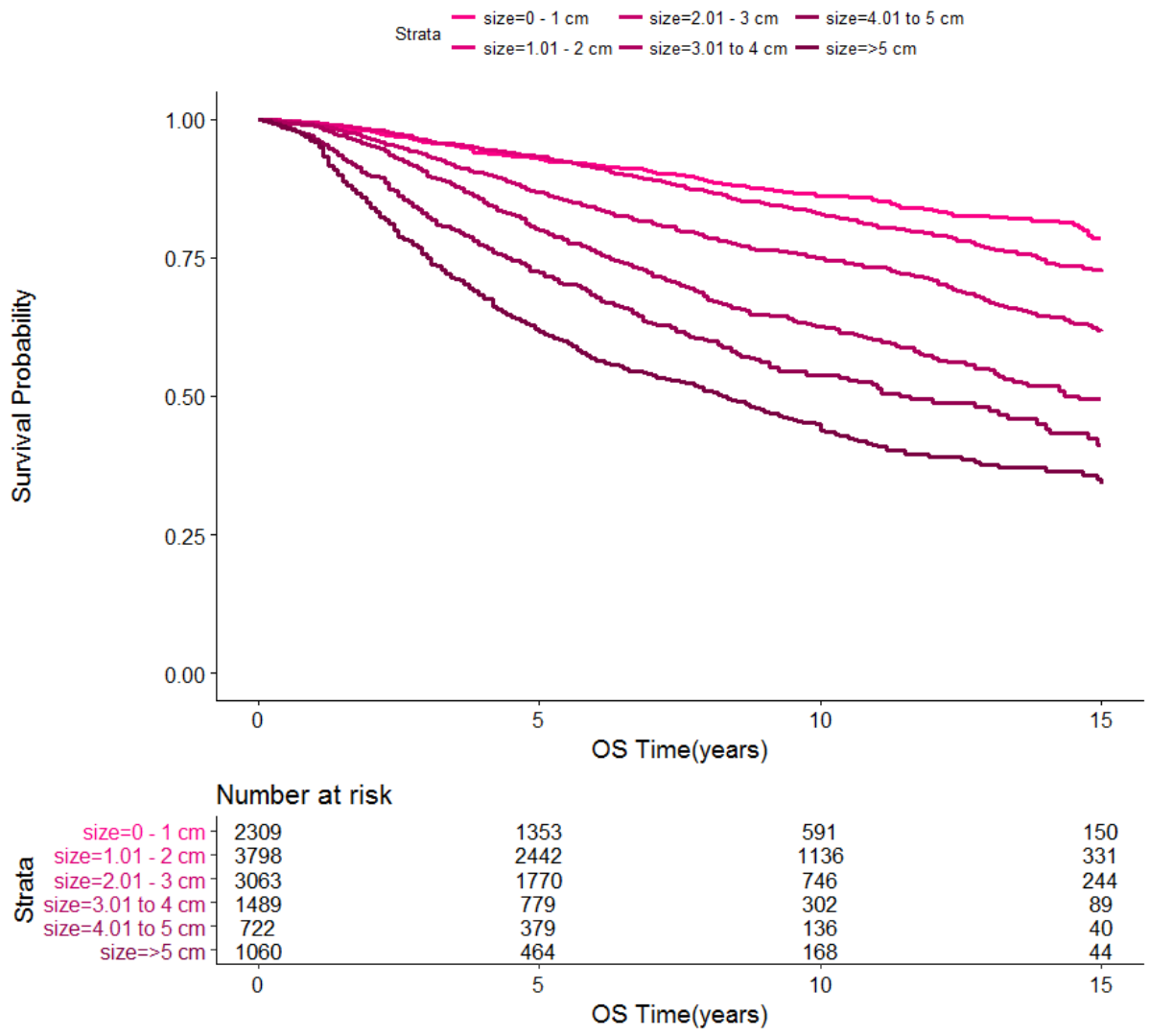


Figure 6-5. Overall survival by tumour size group.

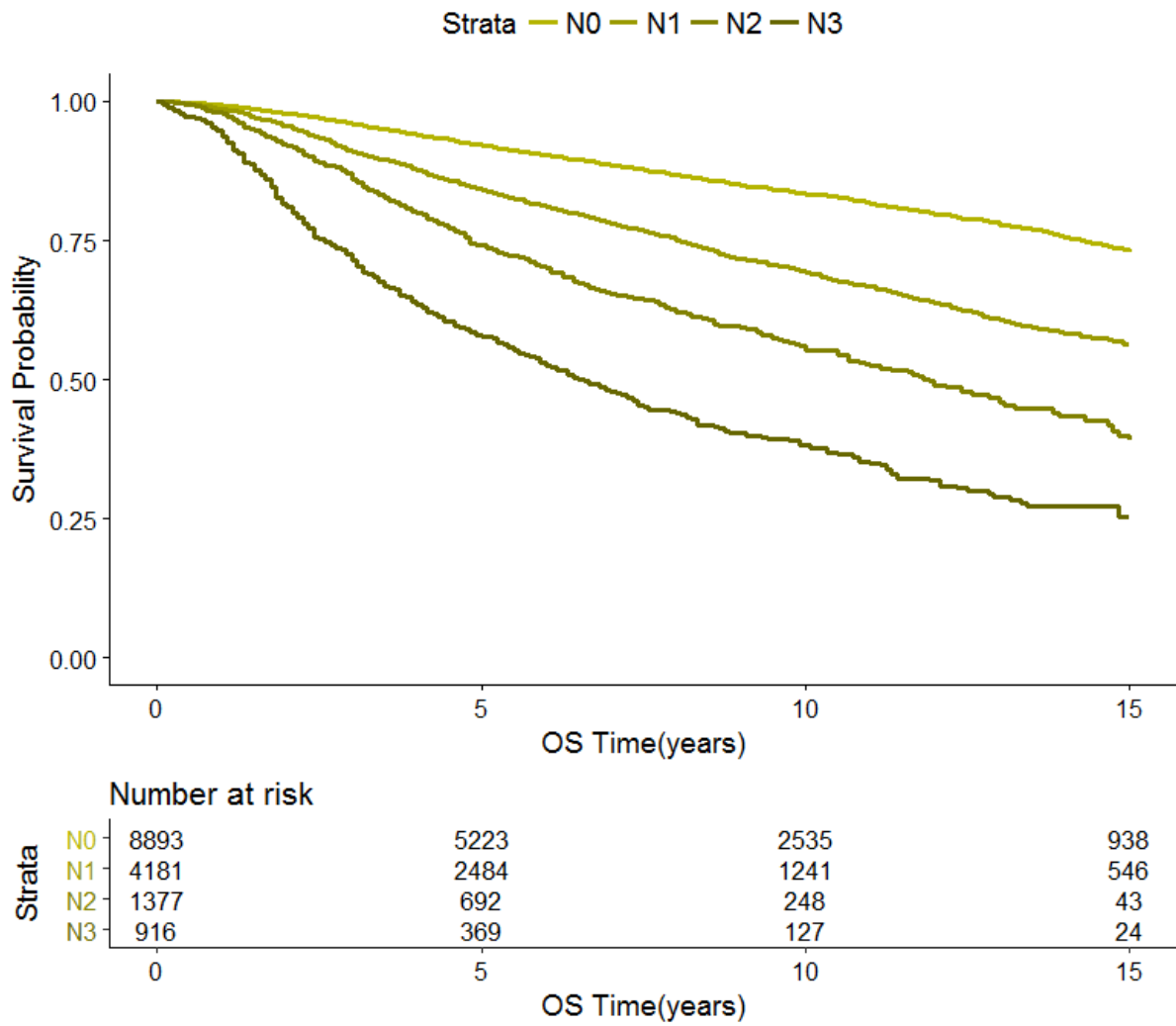


Figure 6-6. Overall survival by nodal stage.

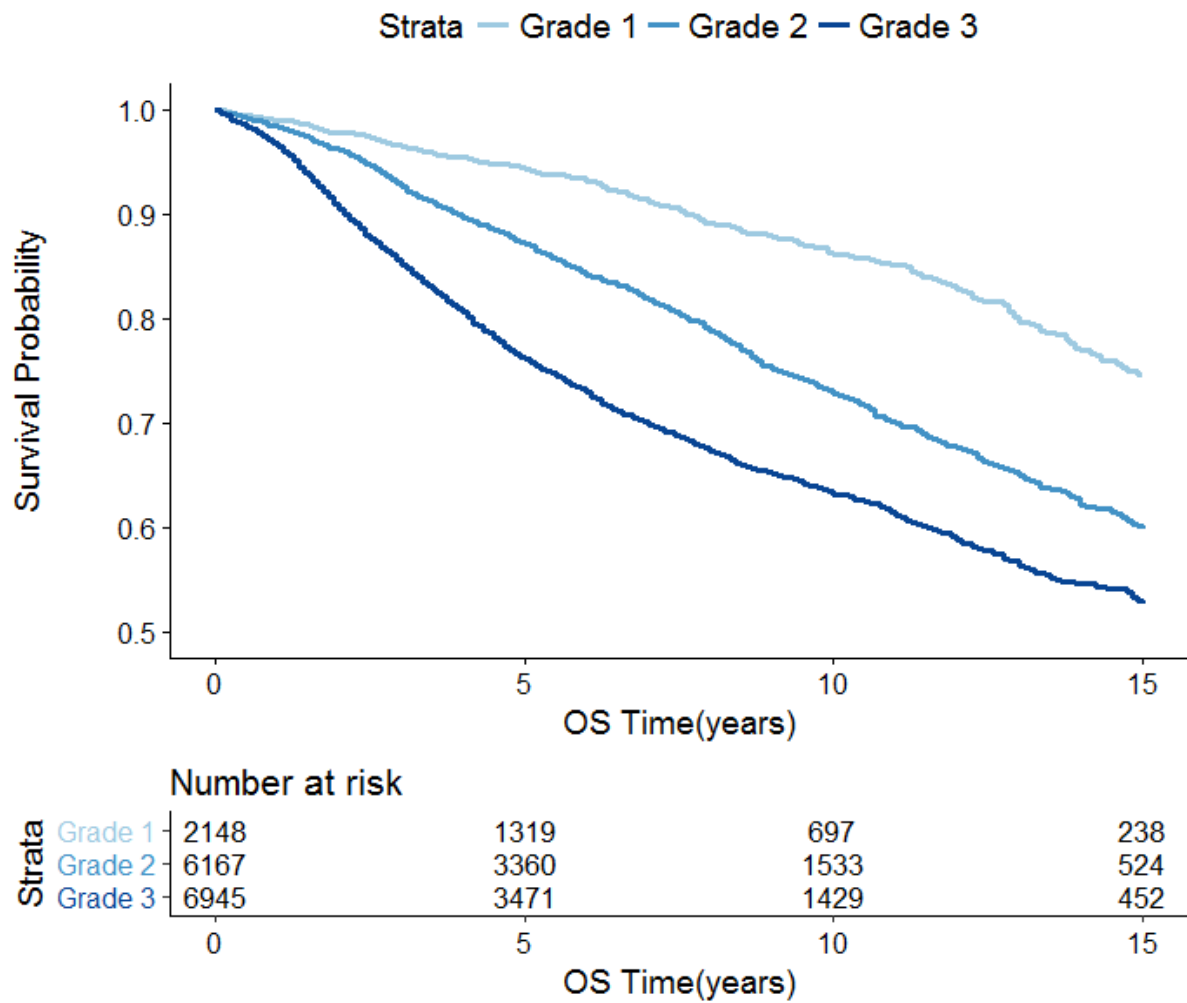
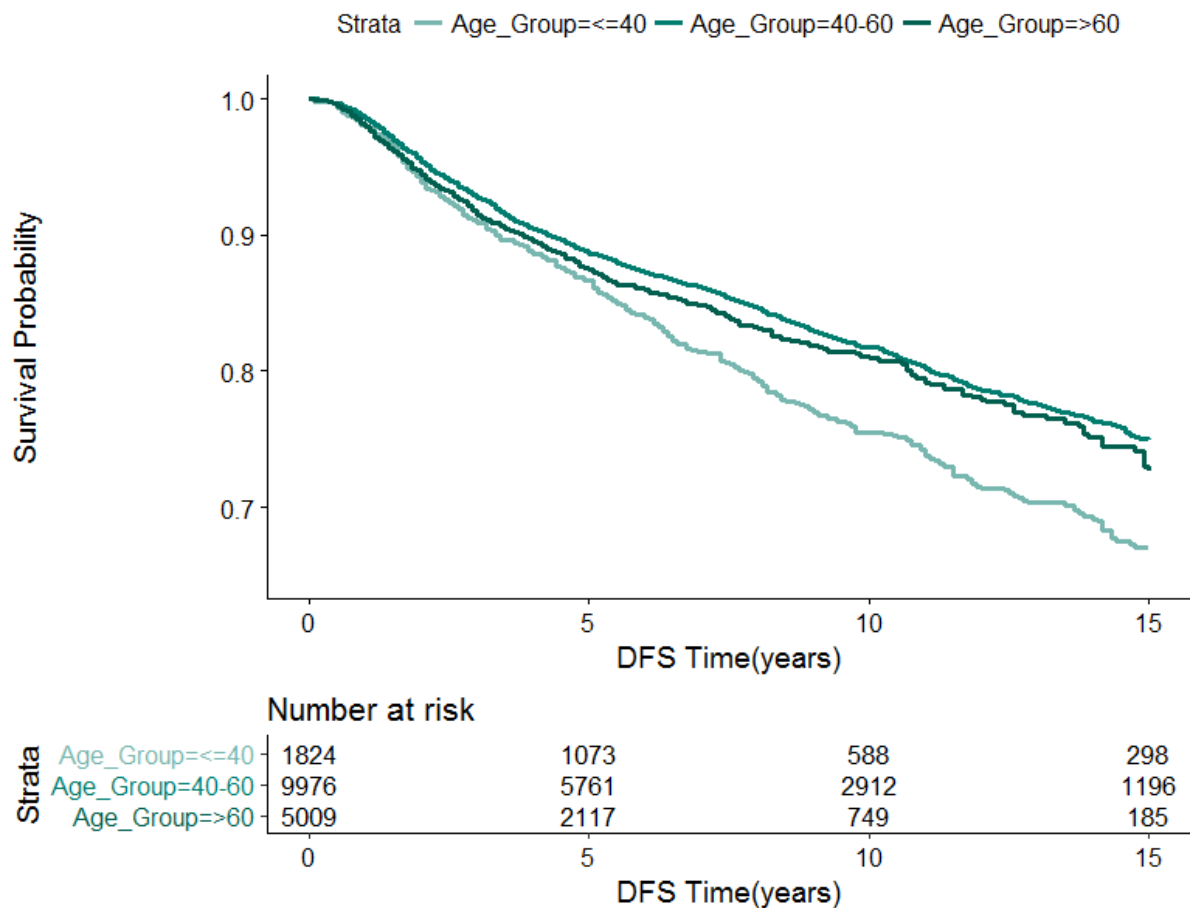


Figure 6-7. Overall survival by grade differentiation.

6.2. Disease Free Survival (DFS)

Young patients below the age of 40 years have a poorer disease free survival as compared to older patients (Figure 6-8). Malays had the lowest disease free survival (Figure 6-9).



Age Group	Number of patients who have metastatic disease at diagnosis
<= 40	119
40 to 60	1044
> 60	738

Figure 6-8. Disease free survival by age group.

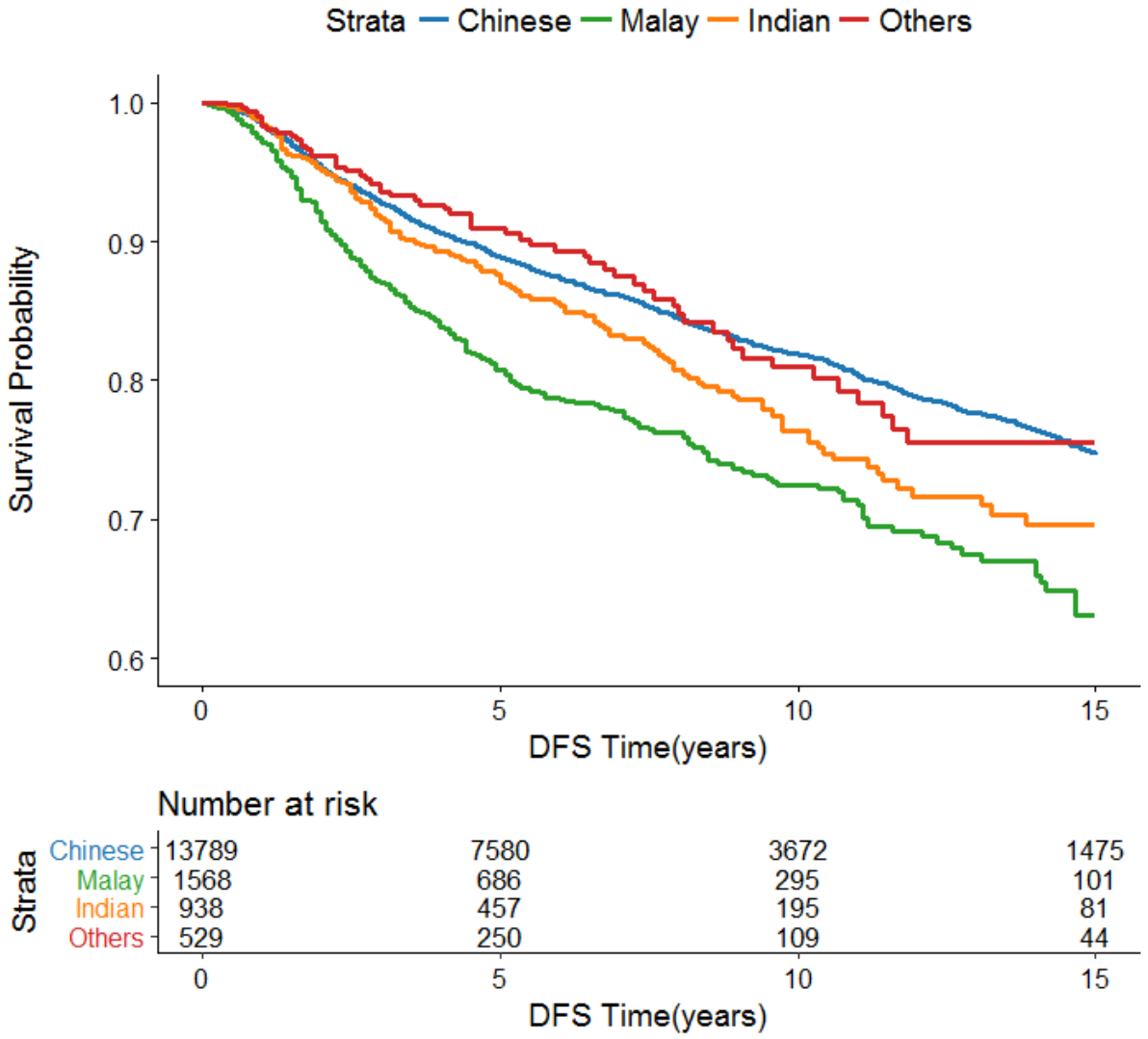


Figure 6-9. Disease free survival by race.

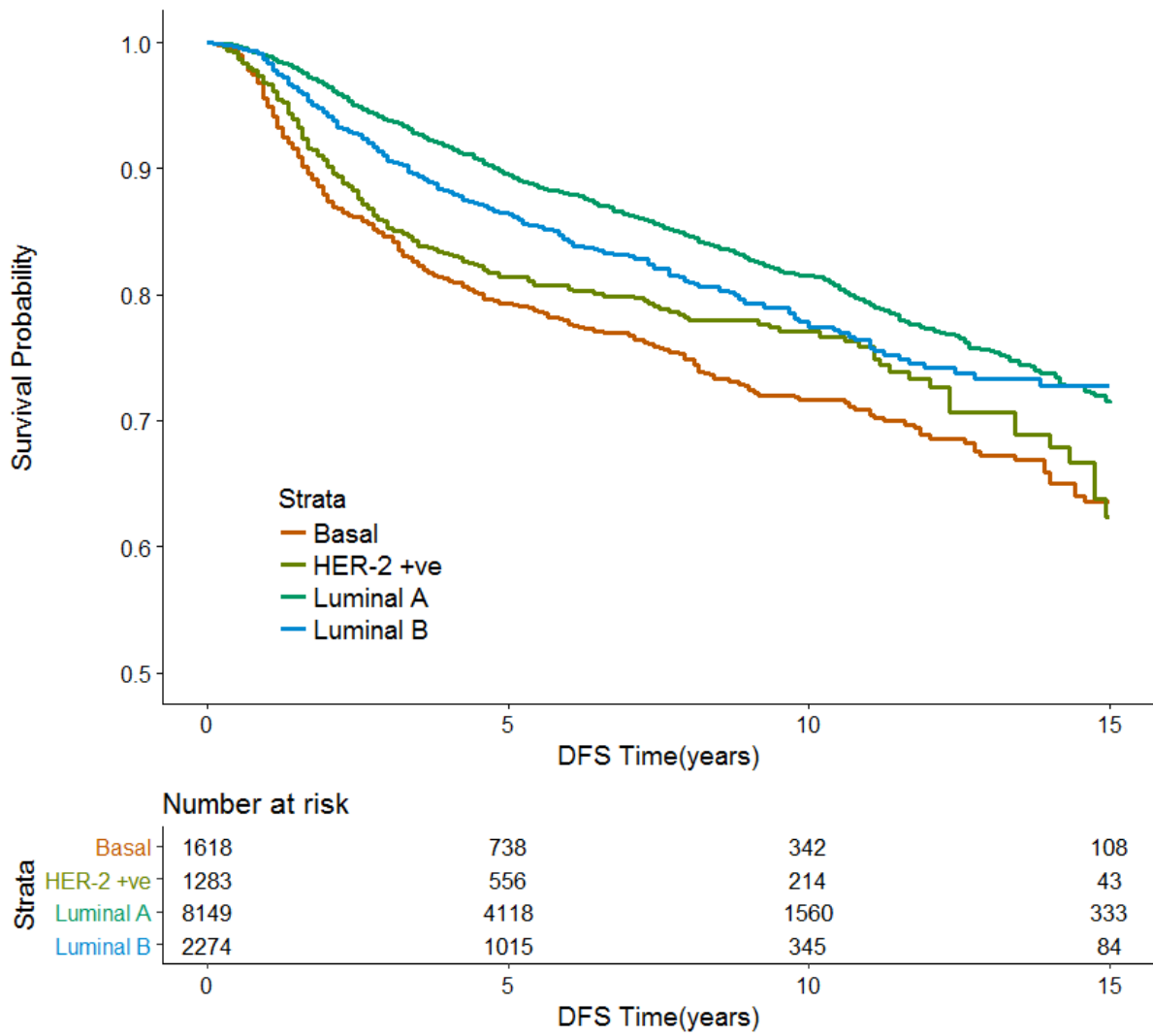


Figure 6-10. Disease free survival by histology subtype.

6.3. Ipsilateral Breast Tumour Recurrence (IBTR)

Patients with higher tumour stage were more likely to experience local recurrences (Figure 6-11). Patients with luminal A or B histology have better local recurrence free survival as compared to those with triple negative or HER-2 positive histology (Figure 6-12). However unlike other histology, the cohort of patients diagnosed with luminal A cancer continue to experience local recurrence progressively even after 15 years of follow up.

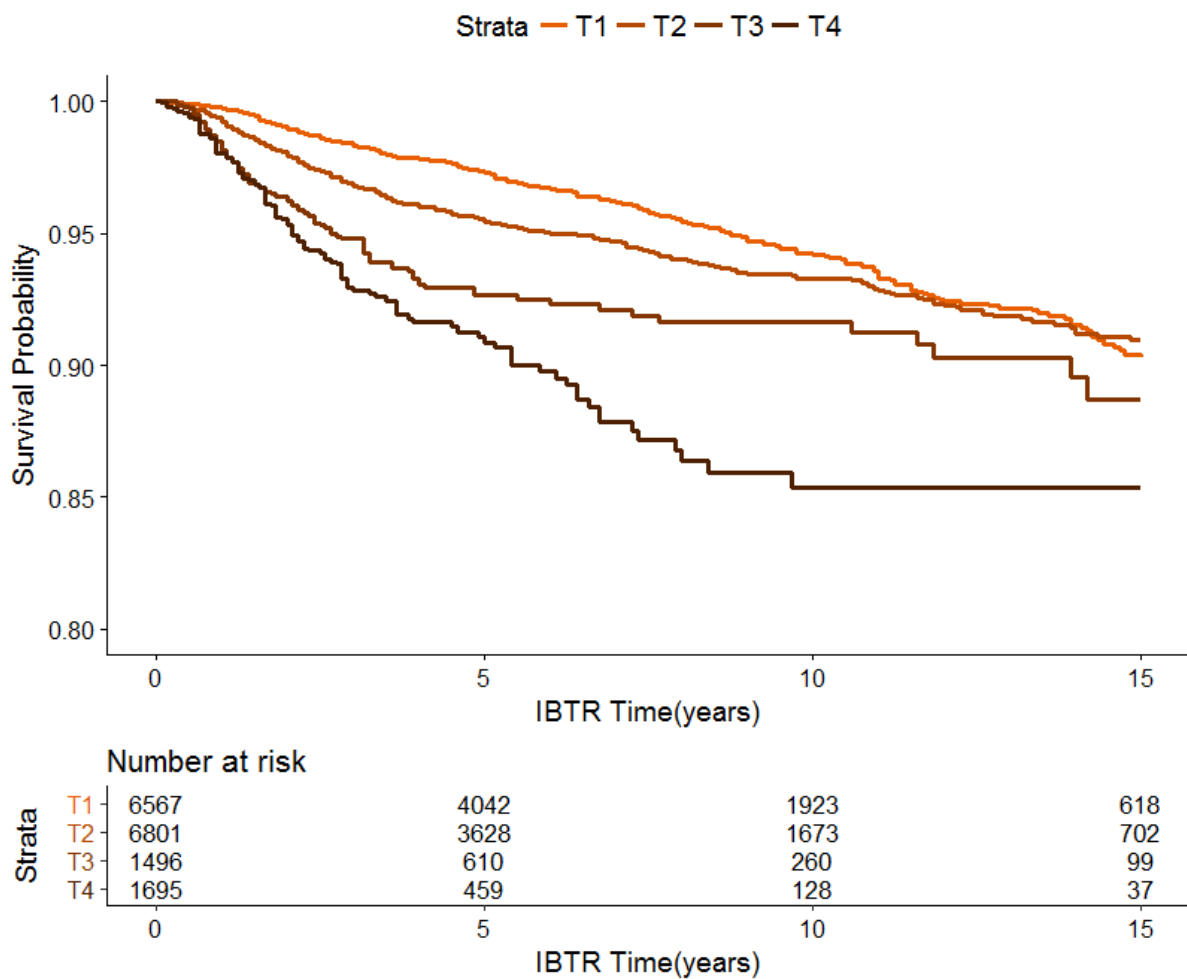


Figure 6-11. Ipsilateral breast tumour recurrence by tumour stage.

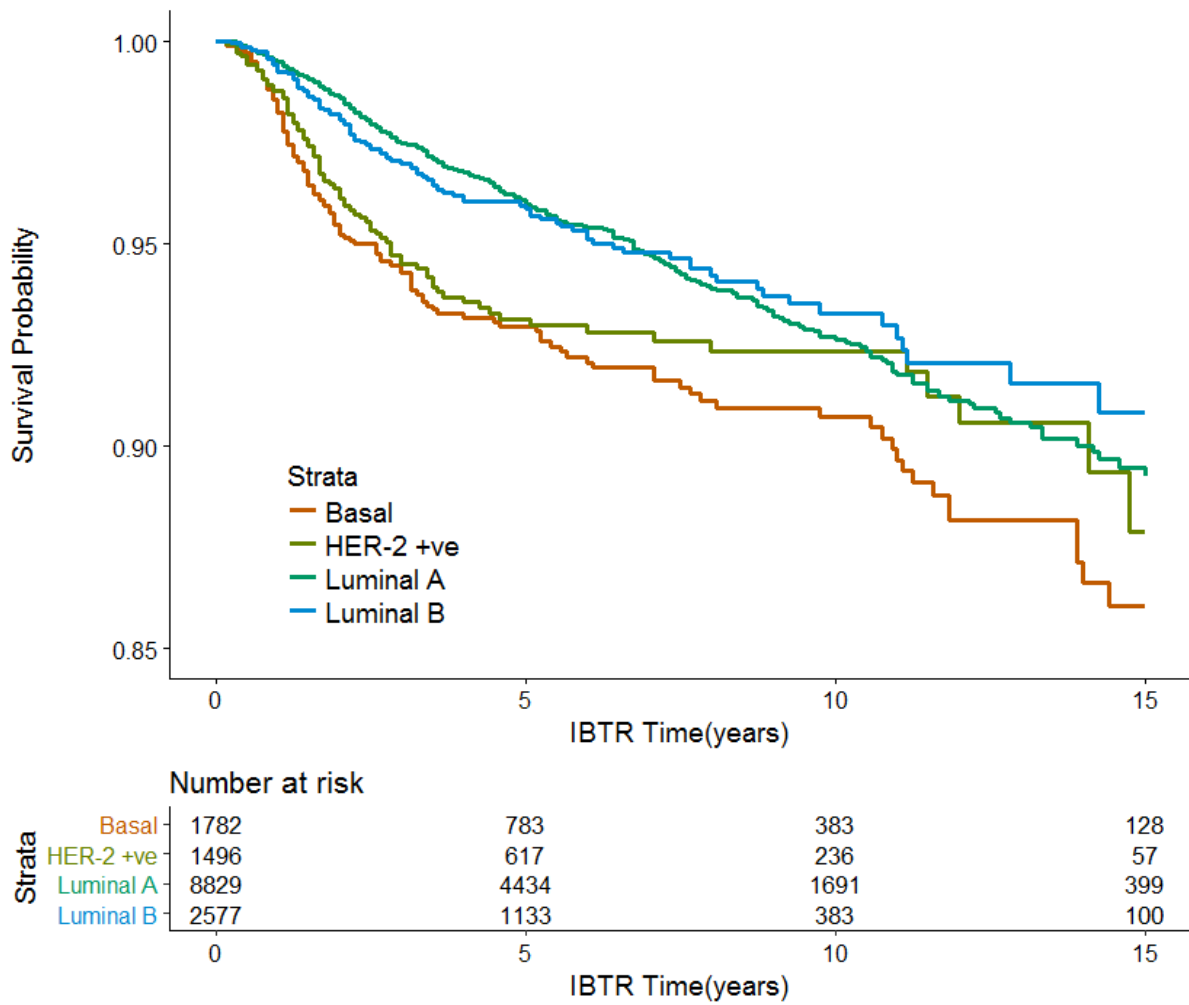


Figure 6-12. Ipsilateral breast tumour recurrence by histology subtype.

6.4. Distant Disease Free Survival (DDFS)

The nodal stage strongly predicted for distant recurrences (Figure 6-13). Among the different histology subtypes, luminal A and B still had better survival than Her-2 and triple negative breast cancer (Figure 6-14).

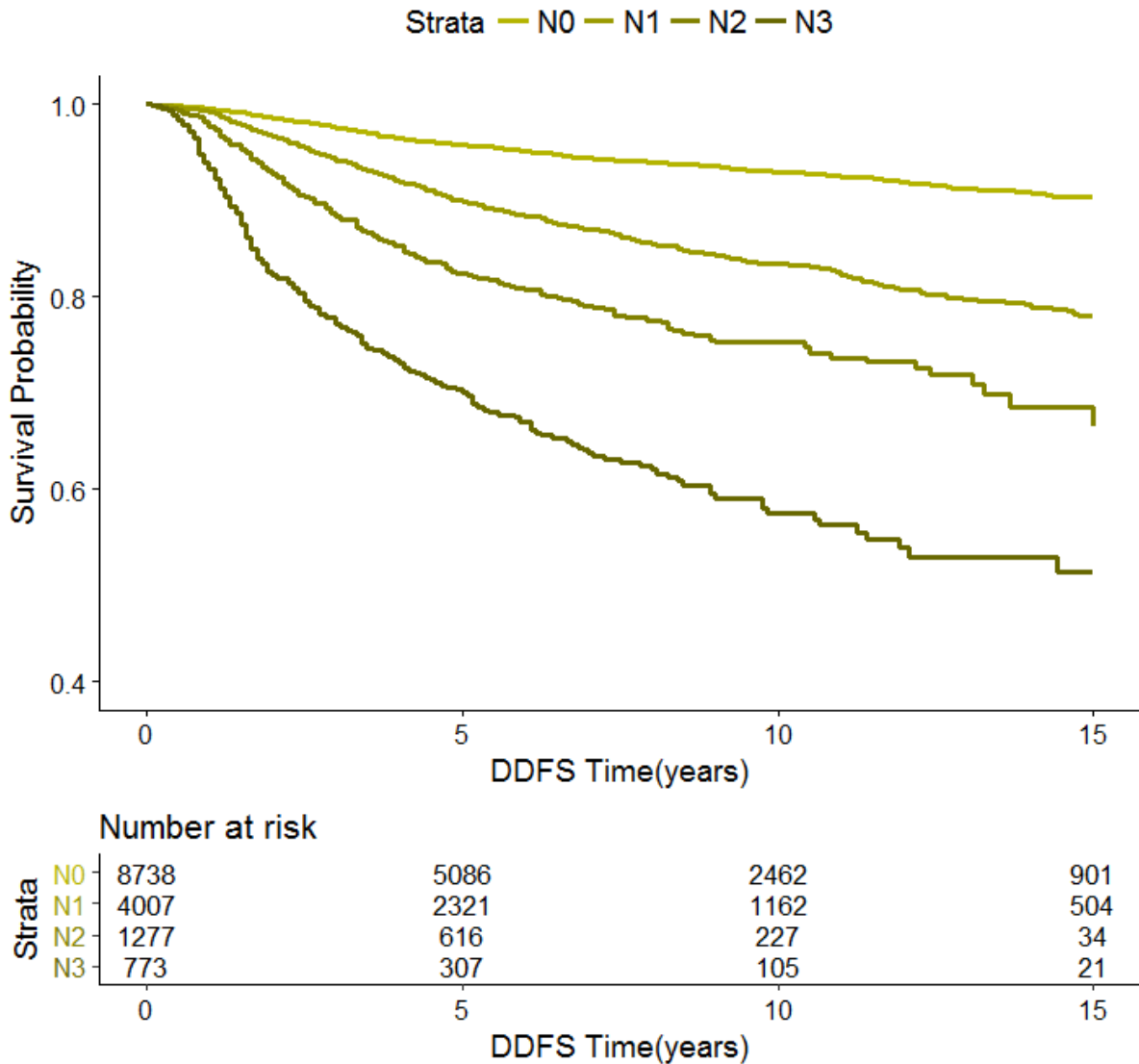


Figure 6-13. Distant disease free survival by nodal stage.

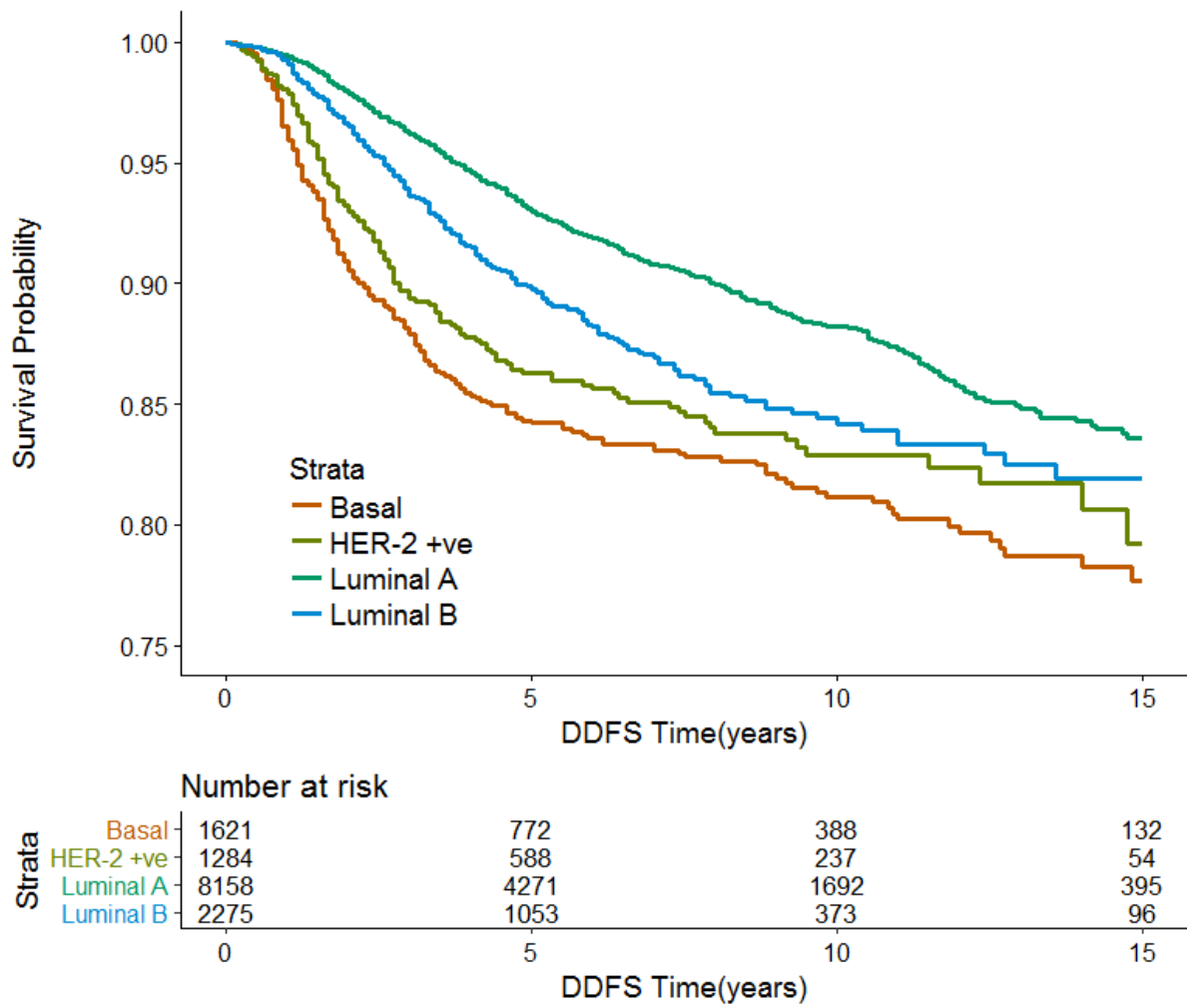


Figure 6-14. Distant disease free survival by histology subtype.

- [NON-INVASIVE CANCER ONLY] -

In the following analyses, patients diagnosed with non-invasive cancers (including ductal carcinoma in-situ) are presented. Any values are rounded to 2 significant figures for clarity purpose.

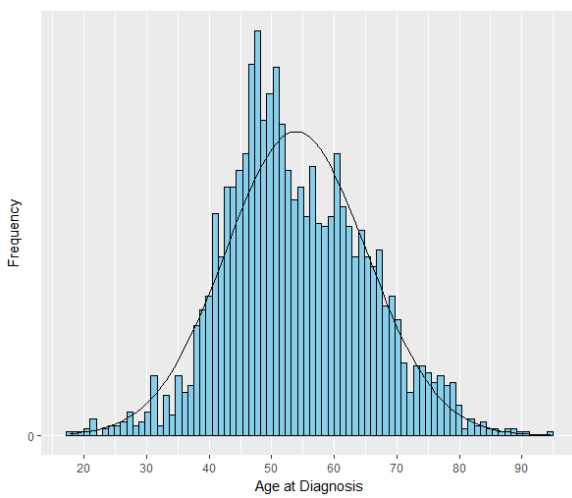
7. Non-invasive cancers

Ductal Carcinoma In-Situ (DCIS) cases are presented separately due to the more indolent nature of the disease. There were about 2,700 DCIS cases, with a median age at diagnosis of 53 years. The median tumour size was 1.5 cm. Most patients diagnosed with DCIS are in their late 40s. 89% of DCIS subjects were Chinese, compared to 81% for IDC. 53% of DCIS were screen-detected. 69% of the reconstructed cases were TRAM flaps.

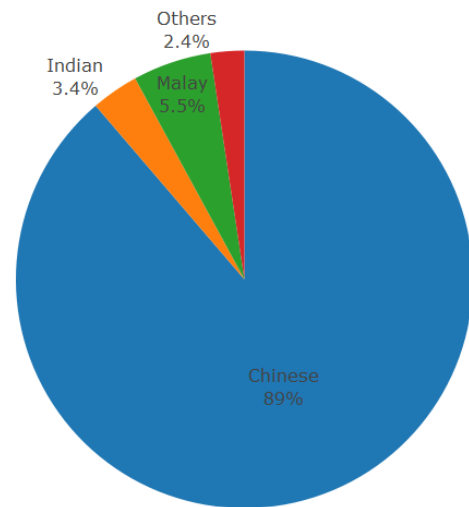
Summary statistics of residential patients diagnosed with non-invasive cancers.

Factor	Mean	SD	Median	1 st Quartile	3 rd Quartile	Min	Max
Age (years)	54	11	53	46	62	18	95
Tumour Size (cm)	1.8	1.6	1.5	0.70	2.5	0	10

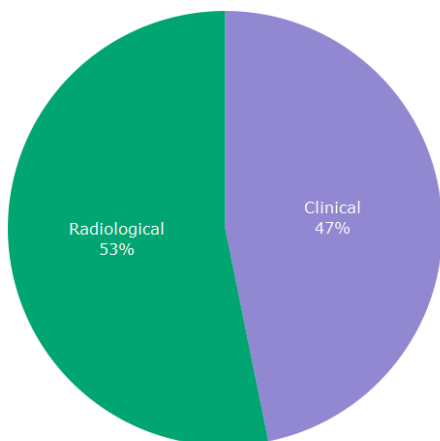
Histogram of Age at Diagnosis
DCIS Cases



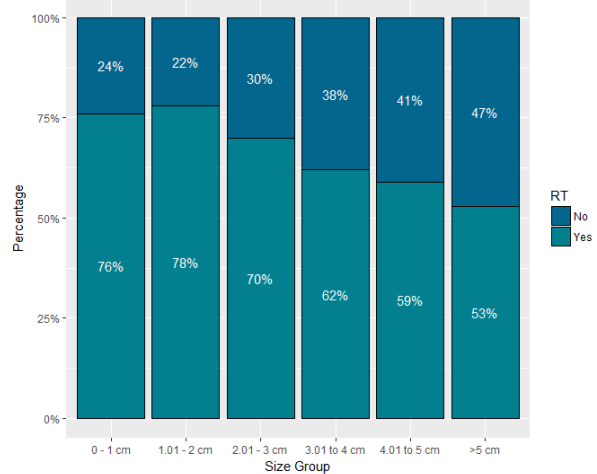
Proportion of DCIS Cases by Race



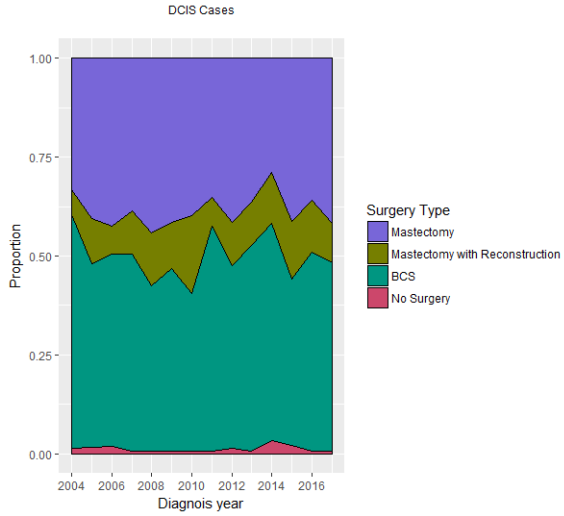
Proportion of DCIS Cases by Presentation



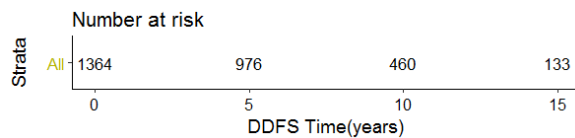
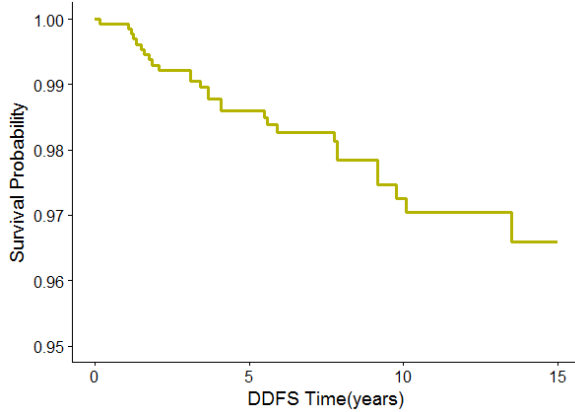
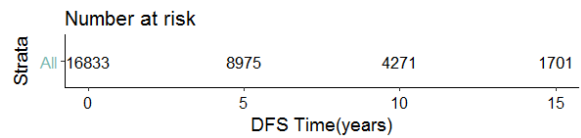
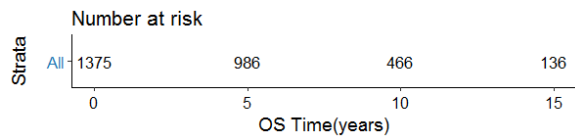
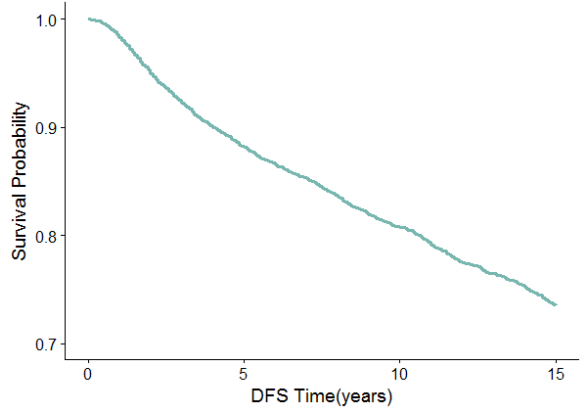
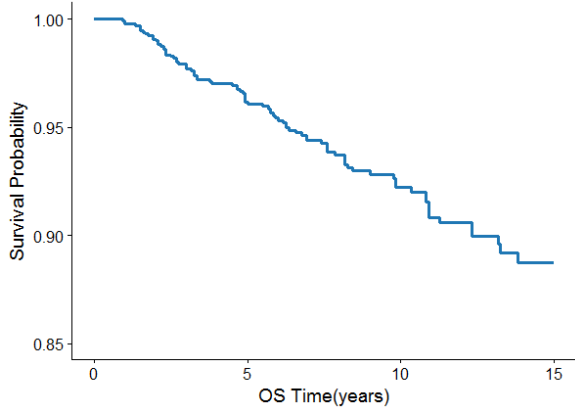
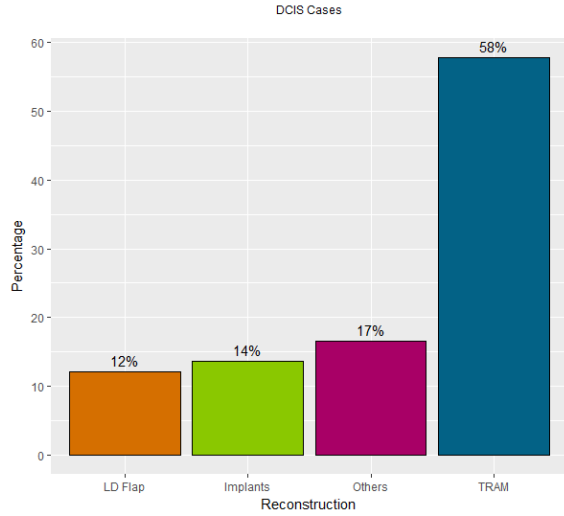
Proportion of DCIS Patients who Received RT by Size Group



Proportion of Surgery Type by Diagnosis Year



Percentage of Cases with Reconstruction



8. Research

8.1. Published Manuscripts

1. Prognostic role of adjuvant radiotherapy in triple-negative breast cancer: A historical cohort study.
Int J Cancer. 2015 Nov 15;137(10):2504-12
2. Clinicopathological characteristics and treatment outcomes in patients with stage I-III invasive Lobular carcinoma of the breast (ILC) treated at the National Cancer Centre Singapore.
2016 ASCO Annual Meeting. J Clin Oncol 2016 suppl; abstr.
Joycelyn Jie Xin Lee, Fuh-Yong Wong, Benita Tan, Swee Ho Lim, Sze Huey Tan, Joanne YY Ngeow, Rebecca Alexandra Dent
3. Outcome after neoadjuvant chemotherapy in Asian breast cancer patients.
Cancer Med. 2017 Jan; 6(1): 173–185. Li Yan Lim, Hui Miao, Joline S.J.Lim, Soo Chin Lee, Nirmala Bhoo-Pathy, Cheng Har Yip, Nur Aishah B.M.Taib, Patrick Chan, Ern Yu Tan, Swe Ho Lim, Geok Hoon Lim, Evan Woo, Yia Swam Tan, Jung Ah Lee, Mabel Wong, Puay Hoon Tan, Kong Wee Ong, Fuh Yong Wong, Yoon Sim Yap, Mikael Hartman
4. Screening uptake differences are not implicated in poorer breast cancer outcomes among Singaporean malay women.
J Breast Cancer. 2017 Jun;20(2):183-191. Xin WR, Kwok LL, Yong WF.
5. Surgery for early breast cancer in the extremely elderly leads to improved outcomes - An Asian population study.
Breast. 2017 Dec; 36:44-48. Lee CM, Zheng H, Tan VK, Tan TJ, Kanesvaran R, Wong FY, Sim YR, Yong WS, Madhukumar P, Ong KW, Tan BK.
6. Validation of the AJCC 8th prognostic system for breast cancer in an Asian healthcare setting.
Breast. 2018 Apr 17;40:38-44. Wong RX, Wong FY, Lim J, Lian WX, Yap YS
7. Breast cancer anatomic staging with biological risk Score is effective and simple to use.
Melbourne International Breast Conference Oct 2018. WX Lian, YH Seow, YS Yap, JHC Lim, FY Wong

8.2. Ongoing Studies

1. Gestational breast cancer outcomes
2. Effect of ethnicity in breast cancer treatment and outcomes
3. Synchronous contralateral axillary metastases from breast cancer
4. Validation of the modified GPA (graded prognostic assessment) in brain metastases for breast cancer
5. Role of radiotherapy in borderline and malignant phyllodes
6. Incidence of radiation induced sarcomas after breast radiotherapy
7. Healthcare expenditure in HER-2 enriched breast cancer
8. Validation of the NHS Predict nomogram

9. Reference

- (2018, 12). Retrieved 12 2018, from Department of Statistics Singapore: <https://www.tablebuilder.singstat.gov.sg/publicfacing/createDataTable.action?refId=14911>
- Cancer Screening*. (2010). Retrieved 12 2018, from Ministry of Health Singapore: https://www.moh.gov.sg/docs/librariesprovider4/guidelines/cpg_cancer-screening.pdf
- Goldhirsch, A, Wood, W. C., Coates, A. S., Gelber, R. D., Thürlimann, B., Senn, H. J., & Panel members (2011). (2011). Strategies for subtypes--dealing with the diversity of breast cancer: highlights of the St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011. *Annals of oncology : official journal of the European Society for Medical Oncology*, 22(8), 1736-47.
- Hortobagyi, G. N., Connolly, J. L., D'Orsi, C. J., B.Edge, S., Mittendorf, E. A., Rugo, H. S., . . . Giuliano, A. (2018). Breast. In *AJCC Cancer Staging Manual, Eight Edition* (pp. 589-636). Chicago, Illinois.
- Kunkler, I. H., Williams, L. J., Jack, W. J., Cameron, D. A., & Dixon, J. M. (2015). Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial. *The lancet oncology*, 16(3), 266-273.
- Wong, R., Wong, F., Lim, J., Lian, W., & Yap, Y. (2018). Validation of the AJCC8th Prognostic System for Breast Cancer in an Asian Healthcare Setting. *Breast*, 38-44.

APPENDIX: List of variables

Properties	Variables		
Demographics	<ul style="list-style-type: none"> Name NRIC Date of Birth Sex Race Marital Status Address 1 Address 2 Postal Code 	<ul style="list-style-type: none"> With consent 	<ul style="list-style-type: none"> Doctor in charge Referral
Patient History	<ul style="list-style-type: none"> Smoker Alcohol 	<ul style="list-style-type: none"> Chest size Cup size Menarche Age Parity Age at First Child Breast Feeding Oral Contraceptive Menopause Status Age at Menopause Hormone Replacement 	<ul style="list-style-type: none"> Presentation
Family History	<ul style="list-style-type: none"> Family History of Breast Cancer 		
Surgery	<ul style="list-style-type: none"> Surgery Date Surgeon Breast Surgery Type 	<ul style="list-style-type: none"> Reconstruction Dichotomous Reconstruction Type 	
Drug Treatment	<ul style="list-style-type: none"> Neo Adjuvant Chemotherapy Given Chemo Regimen 	<ul style="list-style-type: none"> Hormonal Therapy Given Tamoxifen Duration 	<ul style="list-style-type: none"> Targeted Therapy Given Date of First Herceptin

Radiation Therapy	<ul style="list-style-type: none"> • Other Chemo Regimen 	<ul style="list-style-type: none"> • Date of Last Herceptin 	
	<ul style="list-style-type: none"> • Radiation Given • Radiation Start Date • Radiation End Date 	<ul style="list-style-type: none"> • Radiation Field • Breast Dose • Supraclavicular Dose • Axillary Dose • Intra-mammary Dose 	
Toxicity	<ul style="list-style-type: none"> • Date of Assessment • Height • Weight 	<ul style="list-style-type: none"> • Symmetry of Breast • Edema of Breast • Skin Telangiectasia • Arm Edema • Plexus Assessment • Heart Assessment • Lung Assessment • Patient's satisfaction with cosmesis • Doctor's assessment of cosmesis 	
Recurrence	<ul style="list-style-type: none"> • Fail Date • Type of Failure • Site of Metastasis • Status 	<ul style="list-style-type: none"> • Date for DDFS • Date for IBTR • Date for True Local Recurrence • Date for Other Local Recurrence • Date for Nodal Recurrence • Date for Contralateral Recurrence 	

Death Registry	<ul style="list-style-type: none"> • Date of Death • Cause of death • Death from Breast Cancer 		
Patient Visit	<ul style="list-style-type: none"> • First seen date • Last seen date 		
Tumour Characteristics	<ul style="list-style-type: none"> • Date of diagnosis • Tumour Side • Tumour Site • Multi-focality • Multi-centricity • Histology • Differentiation • Size Precise • Size Category • Margins Precise • Margins Category • Extensive Intraductal Component • Comedo Necrosis • Van Nuys Prognostic Index 	<ul style="list-style-type: none"> • Clinical T Stage • Clinical N Stage • Clinical M Stage • Clinical Staging • Pathological T Stage • Pathological N Stage • Pathological M Stage • Pathological Staging • Overall TNM Staging • False Negative SLNB • Non Sentinel Lymph Nodes Removed • Axillary Clearance 	<ul style="list-style-type: none"> • Estrogen Receptor Intensity • Estrogen Receptor Percentage • Estrogen Receptor Status • Progesterone Receptor Intensity • Progesterone Receptor Percentage • Progesterone Receptor Status • HER2 Intensity • HER2 Percentage • HER2 Status • FISH Status • FISH Ratio • Total number of nodes positive • Total number of nodes removed
Lymph Nodes	<ul style="list-style-type: none"> • Sentinel Lymph Node Biopsy • Number of Sentinel Nodes Positive • Number of Sentinel Nodes Removed 		