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碩士論文

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美國癌症聯合委員會分期系統有效性評估：第7版和第8版比較分析

Assessment of the Effectiveness of the AJCC Cancer Staging System: A Comparative Analysis of the 7th and 8th Editions

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誌謝

兩年的時光飛快，碩班時間的點點滴滴依舊歷歷在目，在台灣與京都兩地的學習可以說是我人生中非常美好的一段時光。要在兩年內完成兩個碩士學位，除了需要大量的時間與精力管理，也需要身邊的老師、家人與助教與同學們的支持，由衷的感謝身邊的人們一路以來的支持與鼓勵。

本文的誕生需要回溯至大學期間我進行專題的時光，大學時期我跟隨著李文宗教授的步伐展開了與癌症登記相關的研究，也很幸運的在李老師與江濬如老師的指導下完成了我人生中第一篇論文的發表。雖然是短篇論文，但對當時作為大學生的我來說依然是一個非常好的里程碑。

隨著上一篇論文的結束，也開啟了這一篇論文的研究，這一篇論文雖看篇幅似乎不長，但也足足跨了我大學與碩班的時光。一開始和老師探討設定的研究方法在不斷的交流與修正之後，最終確立了本論文的研究方法，可以說這篇論文也是透過不斷試錯的過程而誕生的。在這過程中，我非常感謝李老師的精心指導。這三年來，我在研究中遭遇的各種困難，都是在與李老師的討論中找到了解決方案。在論文撰寫的後期階段，李老師在選用措辭方面也給予我許多寶貴建議，尤其是在我們在論文寫作的最後階段，即使李老師因病休養，仍然不辭辛勞地指導我們，對此我感激不盡。

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中文摘要

背景及目的

美國癌症聯合委員會（AJCC）的分期手冊在全球被廣泛認可且經過定期的修訂。本研究旨在評估比較 AJCC 第 8 版與第 7 版在台灣癌症分類上的表現。

方法

本研究利用台灣癌症登記資料，納入 2017 年（AJCC 第 7 版）和 2018 年（AJCC 第 8 版）診斷的癌症病例，進行 2 年的追蹤。使用 ROC （receiver operating characteristic）曲線下面積（area under the curve, AUC）和基於 Lorenz 曲線的 Gini 係數進行評估。

結果

在研究的 20 個癌症部位/亞型中，根據 ΔAUC 或 ΔGini，我們發現口咽癌、肝癌、非小細胞肺癌、前列腺癌在 AJCC 第 8 版的分期表現上有顯著的改善。在口咽癌的患者中，第 1 期患者的兩年存活率增加，而 4A 和 4C 期患者的兩年存活率下降。肝癌的兩年存活率在第 8 版中隨著癌症期別越高而降低，但在第 7 版中，3B 期患者的存活率（15.7%）甚至低於 3C 期（28.7%）和 4A 期（16.2%）。第 8 版在非小細胞肺癌上實現了更精細的預後分期，分離出 1A1、1A2 和 1A3 期，並辨別出較沒那麼嚴重的 4A 期患者。前列腺癌在第 7 版中有 26.4%的 4 期患者可以重新分類為第 8 版的 3 期或 4A 期，分離出來的患者的存活率都超過 90%。

結論

我們的研究結果發現 AJCC 分期系統第 8 版的修訂對台灣的口咽癌、肝癌、非小細胞肺癌和前列腺癌存活曲線的分離產生了正面的影響。

關鍵字：

AJCC 分期系統、癌症分期、台灣癌症登記、AUC、Gini 係數、兩年存活率、癌症預後

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Abstract

Background:

The American Joint Committee on Cancer (AJCC) staging manual is globally recognized and regularly revised. This study aims to evaluate the effectiveness of the AJCC 8th edition compared to the 7th edition in Taiwan.

Methods:

Data from the Taiwan Cancer Registry were utilized for this study. Cancer cases diagnosed in 2017 (AJCC 7th edition) and 2018 (AJCC 8th edition) were included, and follow-up for 2 years. The performance was assessed using the area under the receiver operating characteristic curve (AUC) and the Lorenz curve-based Gini index.

Results:

Among the 20 cancer sites/subtypes studied, 4 cancers (described below) showed significantly improved performance in the 8th edition, as indicated by ΔAUC or ΔGini. For the 2-year survival rates of oropharyngeal cancer, the rate increased for stage 1 patients and decreased for stage 4A and 4C patients. The survival rates for liver cancer decreased with advanced stages in the 8th edition, but in the 7th edition, the rate in 3B (15.7%) was even lower than those in 3C (28.7%) and 4A (16.2%). For non-small cell lung cancer, the split-out stages 1A1, 1A2, and 1A3 had achieved a more refined prognostic staging in the 8th edition, and the split-out stage 4A had identified a group of patients with a less dire prognosis. For prostate cancer, 26.4% of 7th‘s stage 4 patients could be reclassified as 8th’s stage 3 or stage 4A, with a survival rate exceeding 90%.

Conclusions:

Our study findings demonstrate that the revisions in the 8th edition of the AJCC staging system had a positive effect on the separation of survival curves for oropharyngeal, liver, non-small cell lung, and prostate cancer in Taiwan.

Keywords: AJCC staging system, cancer staging, Taiwan Cancer Registry, AUC, Gini index, 2-year survival rates, cancer prognosis

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Introduction

Cancer staging plays a pivotal role in enabling healthcare professionals to assess the scope of cancer within the body and its potential for metastasis. Furthermore, it furnishes essential data that inform treatment choices and facilitates precise prognosis and outcome prediction. The American Joint Committee on Cancer (AJCC) staging manual holds global recognition as a benchmark for cancer staging and is extensively adopted by numerous countries, such as the United States, Canada, Australia, and Taiwan. This widespread utilization of the AJCC staging system ensures its significant impact on clinical practice, research, and treatment strategies.

The AJCC staging manual undergoes regular revisions every 6-8 years to maintain the stability and effectiveness of the cancer staging system. These revisions are driven by the discovery of new research findings and advancements in our understanding of prognostic factors in cancer. The revision process involves extensive collaboration and input from experts in clinical oncology, cancer registries, population surveillance, and statistical communities to ensure the accuracy and relevance of the updates. The most recent edition of the AJCC staging manual is the 8th edition, announced in 2017 and implemented in 2018.

In this study, we utilized data from the Taiwan Cancer Registry (TCR), a nationwide population-based registry, to assess the effectiveness of the latest revision of

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the AJCC staging system. The TCR is known for its commitment to maintaining high-quality data, including accuracy and completeness [1,2]. Additionally, the TCR places a strong emphasis on data timeliness, ensuring that diagnosed cases from 2018 have been fully collected and are available for 2 years of follow-up analysis. This timeliness enables us to make a timely comparison of the staging performances between the AJCC 7th edition (patients diagnosed in 2017) and the AJCC 8th edition (patients diagnosed in 2018) staging systems.

Materials and Methods

This study utilized data from the TCR. Cancer staging was performed according to AJCC Staging Manual 7th edition before 2018 and AJCC 8th edition in and after 2018. Cancer patients diagnosed in 2017 and 2018 were included in our analysis, and a comprehensive 2-year follow-up was conducted for all patients. A total of 20 cancer sites/subtypes were studied (Table 1, International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) in Appendix Table 1). We relied on the overall stage of the TNM staging system, considering both clinical and pathological aspects. Hematologic malignancies were excluded because the TNM staging system is not pertinent to them.

We used the area under the receiver operating characteristic curve (AUC) [3] to

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compare the performances of the AJCC 7th and AJCC 8th staging systems. Let n_1 be the number of patients who died within two years of cancer diagnosis (indexed from 1 to n_1) and n_2 be the number of patients who survived beyond that time interval (indexed from n_1+1 to n; $n = n_1 + n_2$). The formula for AUC is

$$\text{AUC} = \frac{\sum_{i=1}^{n_1}\sum_{j=n_1+1}^{n} S(i,j)}{n_1 \times n_2},$$

where, $S(i,j) = 1$ if the ith patient has a more advanced cancer stage than that of the jth patient, $S(i,j) = 0.5$ if they are of the same stage, and $S(i,j) = 0$ if the ith patient has an earlier cancer stage than the jth patient. AUC is the probability that a randomly selected patient who died has a more advanced cancer stage than a randomly selected patient who survived [4][5].

We also used the Lorenz curve-based Gini index to compare the two versions of AJCC. The formula for Gini is

$$\text{Gini} = \frac{(\sum_{i=1}^{n}\sum_{j=1}^{n}|p_i - p_j|)/n^2}{2 \times \bar{p} \times (1-\bar{p})},$$

where p_i is the probability of death within two years of cancer diagnosis (one minus 2-year survival rate) for the ith patient after staging and $\bar{p}(\bar{p} = n_1/n)$ is the probability of death within two years of cancer diagnosis before staging. The numerator of Gini is the average absolute difference in the probability of death of two randomly selected patients, and the denominator is the same value for a perfect staging system that predicts a patient that dies with a death probability of 1 and a patient that survives with a

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probability of 0 [$\bar{p} \times (1-\bar{p}) \times |1-0| + (1-\bar{p}) \times \bar{p} \times |0-1| = 2 \times \bar{p} \times (1-\bar{p})$] [4][5]. Hence, Gini measures how well the staging system separates the patients in terms of their prognosis relative to a perfect staging system.

To evaluate the performance differences between the AJCC 7th and 8th edition staging systems, we defined ΔAUC as the change in AUC from 2017 to 2018 and ΔGini as the analogous difference for Gini. We employed the bootstrapping method to estimate the 95% confidence intervals for ΔAUC and ΔGini. Specifically, we randomly sampled with replacement to derive two new datasets from the original 2017 and 2018 datasets. From these, we calculated the AUCs (and Gini values) and determined their differences to arrive at ΔAUC (and ΔGini). This process was iterated over 1000 bootstrapping simulations. The 2.5th and 97.5th percentiles of the bootstrapped differences established the 95% confidence intervals for ΔAUC and ΔGini. Given that AUC and Gini have different ranges, we computed the effect size for ΔAUC (and ΔGini) as the ratio of the mean to the standard deviation from the bootstrapped samples of ΔAUCs (and ΔGini's) to ease comparisons.

For cancer sites/subtypes that showed a significant difference in the performance of the staging system in AJCC 7th and 8th editions (ΔAUC or ΔGini significantly different from zero), we used the Kaplan-Meier method to plot the survival curves by stage for the two staging systems.

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Results

Table 1 compares the performance of the staging system in AJCC 7th and 8th editions. For oropharyngeal cancer, non-small cell lung cancer, and prostate cancer, the associated ΔAUC and ΔGini are both significantly larger than 0. For liver cancer, the ΔAUC is significantly larger than 0 (with an effect size of 2.056), but the ΔGini is not significantly different from 0 (effect size=1.547). For the other cancer sites/subtypes (oral cavity cancer, hypopharyngeal cancer, salivary gland cancer, nasopharyngeal cancer, esophageal cancer, stomach cancer, colorectal cancer, rectal cancer, intrahepatic bile duct cancer, laryngeal cancer, small cell lung cancer, breast cancer, cervical cancer, corpus uteri cancer, ovarian cancer, and bladder cancer), neither the ΔAUC nor the ΔGini is significantly different from 0.

The AJCC 7th and 8th editions for oropharyngeal cancer have the same stages (1, 2, 3, 4A, 4B, and 4C). In both editions, the 2-year survival rates for oropharyngeal cancer decreased with more advanced stages (Table 2). Comparing the AJCC 8th edition with the 7th edition, the proportion of patients in stage 1 increased (from 18% to 28%), that in stage 4A decreased (from 39% to 22%), and the remainder remained approximately the same (Table 2). As for the 2-year survival rates, the rate increased for stage 1 patients (from 80.1% to 84.8%), decreased for stage 4A (from 58.5% to 50.9%),

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and 4C (from 22.0% to 10.0%) patients and remained roughly the same for the other stages. The survival curves were more separated when staged by the AJCC 8th edition than the 7th edition (Figure 1).

The AJCC 8th edition for liver cancer revises the 7th edition by splitting stage 1 into two (1A and 1B) and combining 3B and 3C into one (3B) (Table 2). However, the revision may also cause some patients to down-stage from stage 2 to stage 1A (Appendix Figure 1). The 2-year survival rates for liver cancer decreased with more advanced stages when staged by the AJCC 8th edition, but by the 7th edition, the rate in 3B (15.7%) was even lower than those in 3C (28.7%) and 4A (16.2%) (Table 2). The proportion of patients in stage 1A/1B in the AJCC 8th edition (14%+25%=39%) was roughly the proportion in stage 1 in the 7th edition (40%). Effectively, the AJCC 8th edition has re-classified the stage 1 patients in the 7th edition with fair prognosis (2-year survival rate=81.6%) into those who were even better (84.8%; stage 1A in the 8th edition) and the rest who were worse (78.9%; stage 1B in the 8th edition). The proportion of patients in stage 3B in the 8th edition (16%) equaled that in 3B/3C in the 7th edition (11%+5%). The paradoxical staging results in the AJCC 7th edition (2-year survival rate: 3C>4A>3B) were longer found in the 8th edition (2-year survival rate: 3B>4A). In Figure 1, the survival curve of stage 3B overlaps 4A in the 7th edition, whereas in the 8th edition, the curves of 3B and 4A are separated. The added stage 1A

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and 1B in the 8th edition also contribute to the separation in the survival curves.

The AJCC 8th edition for lung cancer revises the 7th edition by splitting stage 1A into 1A1, 1A2, and 1A3, stage 4 into 4A and 4B, and creating a new stage 3C (Table 2). Patients staged between 1B and 3B in the 7th edition could be up-, equal- or down-staged between 1B and 3C in the 8th edition in a complex manner (Appendix Figure 2). The 2-year survival rates for non-small cell lung cancer decreased with more advanced stages when staged by the AJCC 7th edition (Table 2). In the 8th edition, the split-out stages 1A1, 1A2, and 1A3 (2-year survival rates: 98.8%, 95.4%, and 91.8%, respectively) had achieved a more refined prognostic staging of stage 1A in the 7th edition (2-year survival rate=97.2%), and the split-out stage 4A (3013 patients, accounting for 24% of patients diagnosed in 2018) had identified a group of patients with less dire prognosis: 2-year survival rate (41.3%) fell between the rates in 3B (51.7%) and 3C (36.8%) (Table 2 and Figure 1). The effect sizes comparing AJCC 8th and 7th editions are larger for ΔGini (3.953) than ΔAUC (3.726) (Table 1).

The AJCC 8th edition for prostate cancer produces a more refined staging than the 7th edition (Table 2, Figure 4). Judging from both editions' definitions of the stages, the possible stage migrations from the old edition to the new one are rather complicated (Appendix Figure 3). The 2-year survival rates for prostate cancer in the AJCC 7th edition from stages 1 to 3 were quite similar and above 90%, while the stage 4 patients

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had a comparatively meager 2-year survival rate of 74.3%. Despite the 8th edition's being a more refined staging, in all stages from 1 to 4A, the 2-year survival rates were similar and above 90%. But the stage 4 patients in the 7th edition (1737 patients; 34%) who survived the worst were reclassified in the 8th edition as stage 4B (1470 patients; 25%) with a genuinely low survival (2-year survival rate of 72.2%) and other stages (could be stages 3B, 3C, or 4A; Appendix Figure 2) with a high survival rate (2-year survival rates all above 90%) (Table 2). For prostate cancer, the effect sizes comparing AJCC 8th and 7th editions are also larger for ΔGini (2.173) than ΔAUC (1.954) (Table 1).

Discussion

This study showed that cancer staging performances for oropharyngeal, liver, non-small cell lung, and prostate cancer were significantly improved for patients diagnosed in 2018 (staged with the AJCC 8th edition) than those diagnosed in 2017 (the 7th edition). It is reasonable to assume that in one year, no significant change in medical care can drastically affect patient survival. Hence, any improvements in staging performances between 2017 and 2018 are most likely due to the revisions of the AJCC edition.

This study utilized two staging performance indicators: AUC and Gini. As pointed

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out, AUC is the probability that a randomly selected patient who died (in 2 years) has a more advanced cancer stage than a randomly selected patient who survived. Thus, a staging system with a 2-year survival rate decreasing with stage will have a higher AUC. Meanwhile, Gini measures how well the staging system separates the patients in terms of their prognosis (2-year survival rates)—the index, on the other hand, considers the prognosis separation but not the correct ordering of the staging system. This help explains why for liver cancer, the ΔAUC (but not the ΔGini) is statistically significant (and with a larger effect size). The AJCC 7th edition's staging for liver cancer did not parallel the actual prognosis curtailing its AUC, the 8th edition did not have the same problem, and thus the difference in the AUCs between the two editions was magnified.

Human papillomavirus (HPV) has been identified as a powerful, independent prognostic factor for the survival outcomes of oropharyngeal cancer patients [6,7]. Recognizing this, the AJCC's 8th edition has incorporated HPV infection status into the staging criteria for oropharyngeal cancer. HPV-positive patients, particularly those with no larger than 6 cm lymph nodes, are now often staged lower and primarily categorized as N1. In contrast, HPV-negative patients have a broader categorization, spanning N1 to N2c. These have led to a notable increase in the percentage of patients classified as stage 1 in the 8th edition, from 18% to 28%. The 8th edition can additionally provide distinct survival rate classifications for HPV-positive and HPV-negative patients.

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Another crucial factor considered in the 8th edition for HPV-negative cancer patients is extranodal extension (ENE). ENE often results in patients being classified into a higher stage, elucidating the rise in stage 4B patients from 12% to 16%. Significantly, our study demonstrates that the AJCC 8th edition's incorporation of prognostic factors like HPV and ENE yields a superior staging performance than its predecessor, the 7th edition, with the AUC improving from 0.67 to 0.73 and Gini from 0.35 to 0.46 for oropharyngeal cancer.

Shindoh et al.'s study showed that microvascular invasion did not predict long-term survival for hepatocellular carcinoma patients with tumor sizes less than or equal to 2cm [8]. Based on the results, the AJCC 8th edition created a new stage 1A for such small-sized solitary liver tumors irrespectively of microvascular invasion. For staging larger solitary liver tumors (>2cm), the AJCC 8th edition does consider microvascular invasion: as the new stage 1B if absent microvascular invasion and the original stage 2 if present. This study shows that the revised staging system has achieved a more refined prognostication for early-stage liver cancer patients: 2-year survival rates for 1A, 1B, and 2 were 84.8%, 78.9%, and 74.0%, respectively. Based on another study that evaluated the AJCC 7th edition's staging for hepatocellular carcinoma [9], the AJCC 8th edition combines stages 3B and 3C into stage 3B. This study shows that with such revision, the 2-year survival rate for liver cancer decreases monotonically with the stage

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as desired.

Tumor size plays a significant role in determining the prognosis for lung cancer, as stated by the International Association for the Study of Lung Cancer (IASLC) [10]. AJCC made a crucial adjustment in its 8th edition by refining the tumor size cut-offs for lung cancer staging. Patients previously classified as stage 1A in the AJCC 7th edition were re-categorized into stages 1A1, 1A2, and 1A3 in the 8th edition, employing new size cut-offs at 1 cm and 2 cm. This alteration led to a better differentiation of varying prognoses, as demonstrated in this study. IASLC also showed that introducing a new stage 3C in the AJCC 8th edition distinguishes patients with a worse prognosis from those classified as stage 3B in the AJCC 7th edition [10]. This study concurs: 2-year survival rates in the AJCC 8th edition were 51.7% for 3B and 36.8% for 3C. The AJCC 8th edition also split stage 4 in the AJCC 7th edition into 4A and 4B based on whether multiple extrathoracic metastases occurred in a single organ or involved multiple organs [11]. Given the prognostic difference, we found that the splitting of the stage is justifiable: 2-year survival rates in the AJCC 8th edition were 41.3% for 4A and 30.3% for 4B. However, we found that in the AJCC 8th edition, the prognosis of patients in 3C is even worse than those in 4A.

The 7th edition of the AJCC utilized the Gleason Score, which is the sum of the two most predominant grades of cancerous cells, to stage early-stage prostate cancer.

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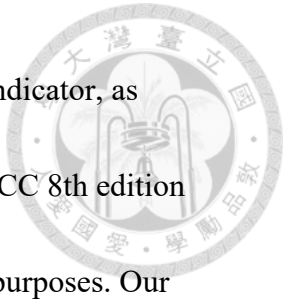

However, this combination of grades resulted in a broad prognostic indicator, as demonstrated in Epstein et al.'s study [12]. In response to this, the AJCC 8th edition now incorporates both components of the Gleason Score for staging purposes. Our findings indicate that the 8th edition offers a more detailed staging system, ranging from stages 1 to 3C, despite the 2-year survival rates for all these stages being similarly high, exceeding 90%. In contrast, the reclassification of late-stage prostate cancer in the AJCC 8th edition has shown a more substantial impact. Patients previously categorized as stage 4 without metastases in the 7th edition are now reclassified as stage 3 (either stage 3B or 3C). Only patients with regional lymph node metastasis and distant metastases can remain in stage 4 (stage 4A for the former and 4B for the latter). In the 7th edition, stage 4 patients had a 2-year survival rate of only 74.3%. However, after reclassification, 26.4% of these patients could be categorized as stage 3 or stage 4A, with a survival rate exceeding 90%. This notable change in staging helped alleviate concerns among patients who mistakenly perceived their cancer as more severe. Our results support the findings of Abdel-Rahman's study, which validated the effectiveness of stage 4 for prostate cancer in the AJCC 8th staging system [13]. However, while Abdel-Rahman et al. conducted retrospective validation, we utilized cancer registry data collected after the implementation of the AJCC 8th edition.

Our study underscores that the changes incorporated into the AJCC’s 8th edition

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staging system enhanced the distinction of stage-specific survival curves for oropharyngeal, liver, non-small cell lung, and prostate cancer in Taiwan. Importantly, our study relies on the latest cancer registry data and incorporates a two-year follow-up duration. However, due to the registry's data collection and coding methodology, we could not directly compare the two AJCC editions on the same patient cohort. Instead, we had to analyze two patient cohorts diagnosed one year apart, with patients diagnosed in 2017 being assessed under the 7th edition and those from 2018 under the 8th edition. Furthermore, further in-depth studies are warranted to gauge the impact of staging revisions on long-term survival outcomes, such as 5-year or 10-year survival rates.

Moving beyond the 8th edition, the AJCC aims to swiftly incorporate the rapid progress in medical research by releasing updates for specific cancers instead of updating all cancer sites collectively, whenever key findings related to cancer treatment and prognosis emerge. We recommend conducting a cancer staging assessment similar to our study following the introduction of any new edition or version. This approach will offer tangible evidence regarding the impact of the changes, informing and guiding future modifications.

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Table 1. Comparison of the staging performances between the 7th and the 8th editions of the American Joint Committee on Cancer Staging Manual (AJCC)

Site of Cancer	AJCC 7th edition (year 2017)			AJCC 8th edition (year 2018)			ΔAUC		ΔGini	
	Number of patients	AUC[a]	Gini	Number of patients	AUC[a]	Gini	estimate (95% CI[b])	effect size	estimate (95% CI[b])	effect size
Oral Cavity	5433	0.734	0.469	5730	0.738	0.476	0.003 (-0.018, 0.023)	0.359	0.007 (-0.036, 0.046)	0.357
Oropharynx	1439	0.673	0.345	1557	0.729	0.458	0.056[c] (0.021, 0.093)	2.963[c]	0.112[c] (0.041, 0.185)	2.957[c]
Hypopharynx	1003	0.659	0.329	1099	0.657	0.317	-0.002 (-0.043, 0.042)	0.160	-0.012 (-0.086, 0.076)	0.261
Major Salivary Glands	292	0.777	0.554	297	0.855	0.716	0.078 (-0.095, 0.265)	1.019	0.162 (-0.133, 0.463)	1.148
Nasopharynx	1365	0.752	0.503	1340	0.752	0.506	0.000 (-0.048, 0.298)	0.387	0.003 (-0.095, 0.199)	0.299
Esophagus	2286	0.734	0.469	2293	0.753	0.514	0.019 (-0.105, 0.046)	0.317	0.045 (-0.169, 0.103)	0.085
Stomach	2866	0.821	0.644	2939	0.832	0.677	0.011 (-0.125, 0.029)	0.540	0.032 (-0.192, 0.072)	0.351
Colon	8004	0.790	0.587	8303	0.793	0.595	0.003 (-0.013, 0.019)	0.402	0.007 (-0.022, 0.038)	0.465
Rectum	4875	0.775	0.563	4762	0.763	0.537	-0.013 (-0.037, 0.011)	1.075	-0.026 (-0.074, 0.020)	1.183
Liver Cell Carcinoma	8263	0.806	0.619	8310	0.820	0.640	0.014[c] (0.001, 0.028)	2.056[c]	0.021 (-0.005, 0.049)	1.547
Intrahepatic Bile Ducts	910	0.834	0.669	990	0.845	0.690	0.010 (-0.031, 0.052)	0.506	0.021 (-0.060, 0.102)	0.552
Larynx	673	0.709	0.419	691	0.769	0.537	0.060 (-0.039, 0.108)	1.058	0.119 (-0.091, 0.213)	1.015
Lung (Small Cell)	827	0.696	0.392	822	0.801	0.601	0.104 (-0.085, 0.369)	0.721	0.209 (-0.109, 0.405)	0.937
Lung (Non-small Cell)	11547	0.799	0.599	12667	0.818	0.639	0.019[c] (0.009, 0.030)	3.726[c]	0.040[c] (0.020, 0.061)	3.953[c]
Breast	13000	0.813	0.627	13302	0.826	0.653	0.013 (-0.015, 0.445)	0.389	0.026 (-0.031, 0.307)	0.542
Cervix Uteri	1123	0.780	0.586	1108	0.821	0.648	0.041 (-0.176, 0.352)	0.602	0.062 (-0.266, 0.198)	0.681
Corpus Uteri	2402	0.855	0.717	2425	0.855	0.715	0.000 (-0.110, 0.201)	0.351	-0.002 (-0.200, 0.398)	0.432
Ovary	1334	0.786	0.580	1358	0.809	0.640	0.023 (-0.216, 0.324)	0.089	0.060 (-0.132, 0.333)	0.601
Prostate Gland	5173	0.696	0.424	5835	0.725	0.482	0.029[c] (0.000, 0.058)	1.954[c]	0.058[c] (0.003, 0.116)	2.173[c]
Bladder	2153	0.746	0.492	2027	0.725	0.451	-0.021 (-0.054, 0.011)	1.313	-0.041 (-0.109, 0.023)	1.308

[a] AUC: area under the receiver operating characteristic curve

[b] 95% CI: 95% confidence interval

[c] Statistically different from zero at a significant level of 0.05

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Table 2. Distribution of the stages of oropharyngeal cancer, liver cancer, non-small cell lung cancer and prostate cancer according to the 7th and the 8th editions of the American Joint Committee on Cancer Staging Manual (AJCC)

Site of Cancer	AJCC 7th edition (year 2017)			AJCC 8th edition (year 2018)		
	stage	number of patients(%)	2-year survival rate	stage	number of patients(%)	2-year survival rate
Oropharynx	**1**	261 (18)	80.1%	**1**	429 (28)	84.8%
	2	197 (14)	73.6%	**2**	268 (17)	71.3%
	3	177 (12)	67.8%	**3**	218 (14)	65.6%
	4A	566 (39)	58.5%	**4A**	350 (22)	50.9%
	4B	179 (12)	35.8%	**4B**	242(16)	36.0%
	4C	59 (4)	22.0%	**4C**	50 (3)	10.0%
Liver Cell	**1**	3265 (40)	81.6%	**1A**	1191 (14)	88.6%
Carcinoma		-	-	**1B**	2098 (25)	78.9%
	2	1961 (24)	74.4%	**2**	2017 (24)	74.0%
	3A	656 (8)	36.0%	**3A**	620 (7)	37.1%
	3B	941 (11)	15.7%	**3B**	1321 (16)	20.9%
	3C	435 (5)	28.7%		-	-
	4A	272 (3)	16.2%	**4A**	275 (3)	12.4%
	4B	733 (9)	7.1%	**4B**	788 (9)	6.9%
Lung (Non-small	**1A**	2687 (23)	97.2%	**1A1**	1759 (14)	98.8%
Cell)		-	-	**1A2**	1182 (9)	95.4%
		-	-	**1A3**	576 (5)	91.8%
	1B	974 (8)	91.1%	**1B**	822 (6)	89.8%
	2A	271 (2)	79.0%	**2A**	126 (1)	81.0%
	2B	204 (2)	69.1%	**2B**	454 (4)	81.3%
	3A	781 (7)	64.0%	**3A**	655 (5)	67.5%
	3B	794 (7)	40.3%	**3B**	598 (5)	51.7%
		-	-	**3C**	304 (2)	36.8%
	4	5836 (51)	33.3%	**4A**	3013 (24)	41.3%
		-	-	**4B**	3178 (25)	30.3%
Prostate	**1**	456 (9)	94.7%	**1**	597 (10)	95.6%
	2A	554 (11)	93.9%	**2A**	314 (5)	94.6%
	2B	1448 (28)	93.0%	**2B**	621 (11)	94.5%
		-	-	**2C**	440 (8)	96.1%
	3	978 (19)	95.5%	**3A**	500 (9)	92.6%
		-	-	**3B**	862 (15)	96.8%
		-	-	**3C**	575 (10)	91.1%
	4	1737 (34)	74.3%	**4A**	456 (8)	92.3%
		-	-	**4B**	1470 (25)	72.2%

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Figure 1. Survival curve of stages of oropharyngeal cancer of the 7th and the 8th editions of the American Joint Committee on Cancer Staging Manual (AJCC)

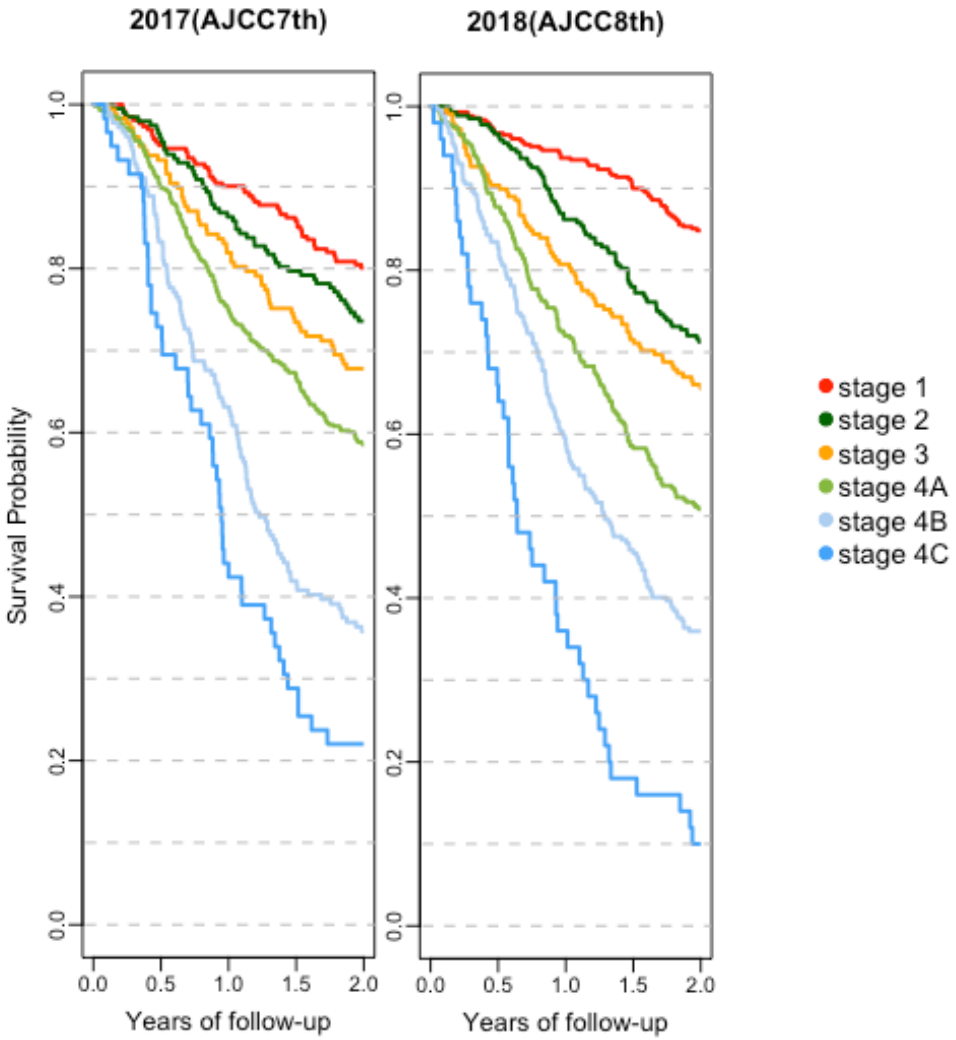

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Figure 2. Survival curve of stages of liver cancer of the 7th and the 8th editions of the American Joint Committee on Cancer Staging Manual (AJCC)

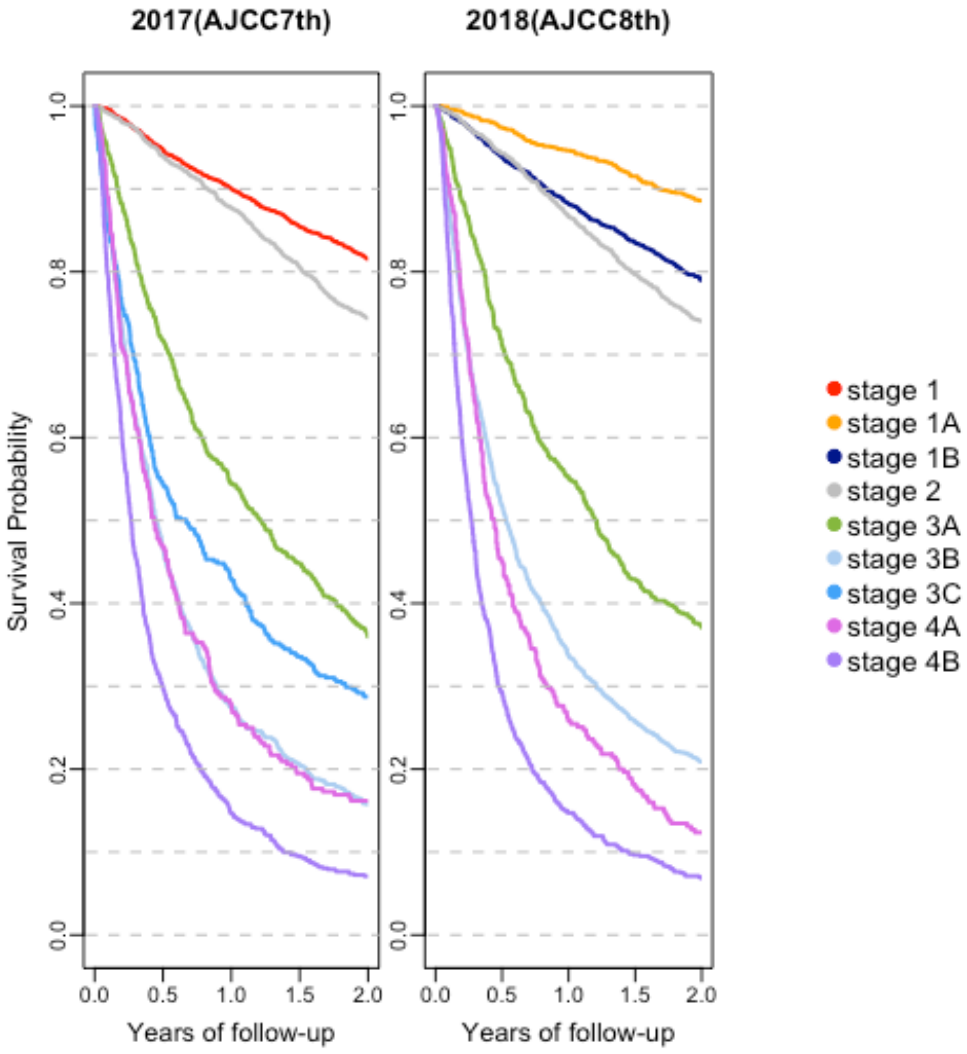

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Figure 3. Survival curve of stages of non-small cell lung cancer of the 7th and the 8th editions of the American Joint Committee on Cancer Staging Manual (AJCC)

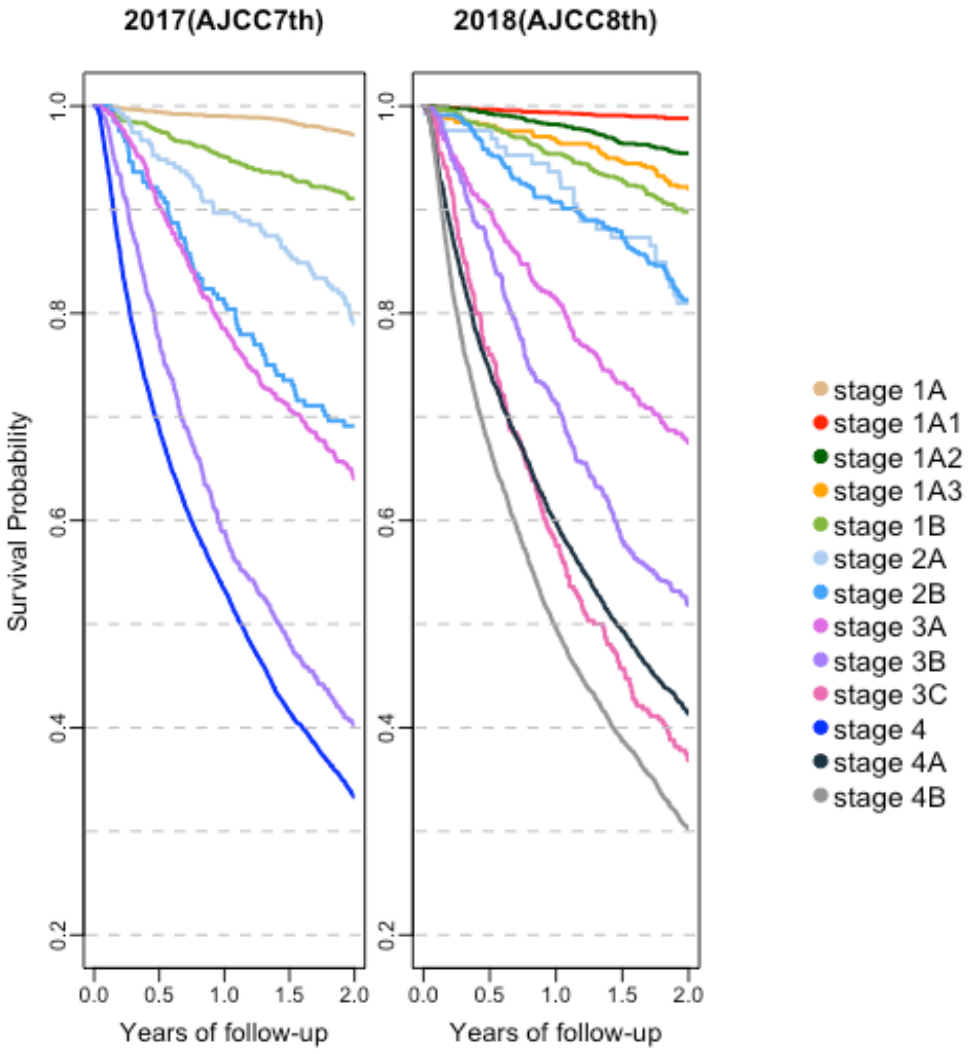

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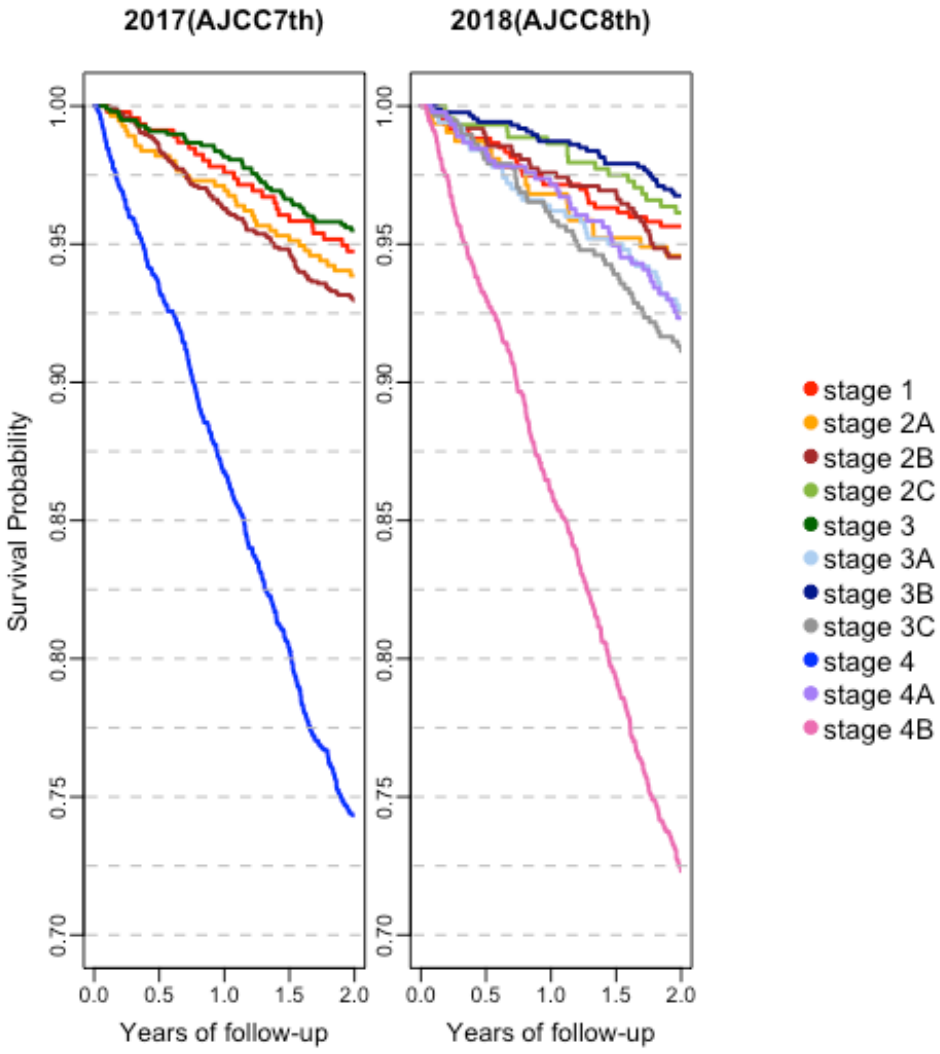
Figure 4. Survival curve of stages of prostate cancer of the 7th and the 8th editions of the American Joint Committee on Cancer Staging Manual (AJCC)



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Appendix Table 1. International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) for 20 cancer sites/subtypes

Site of Cancer	ICD-O-3
Oral Cavity	C00.0, C00.1, C00.2, C00.3, C00.4, C00.5, C00.6, C00.8, C00.9, C02.0, C02.1, C02.2, C02.3, C02.8, C02.9, C03.0, C03.1, C03.9, C05.0, C06.0, C06.1, C06.2, C06.8, C06.9, C04.0, C04.1, C04.8, C04.9, C05.8, C05.9
Oropharynx	C01.9, C02.4, C05.1, C05.2, C09.0, C09.1, C09.8, C09.9, C10.0, C10.1, C10.2, C10.3, C10.4, C10.8, C10.9, C14.2, C14.8
Hypopharynx	C12.9, C13.0, C13.1, C13.2, C13.8, C13.9, C14.0
Major Salivary Glands	C07 - C08
Nasopharynx	C11
Esophagus	C15
Stomach	C16
Colon	C18
Rectum	C19 - C20
Liver	C22.0
Intrahepatic Bile Ducts	C22.1
Larynx	C32
Lung (Small Cell)	C33-C34
Lung (Non-small Cell)	C34.9
Breast	C50
Cervix Uteri	C53
Corpus Uteri	C54 - C55
Ovary	C56
Prostate Gland	C61
Bladder	C67

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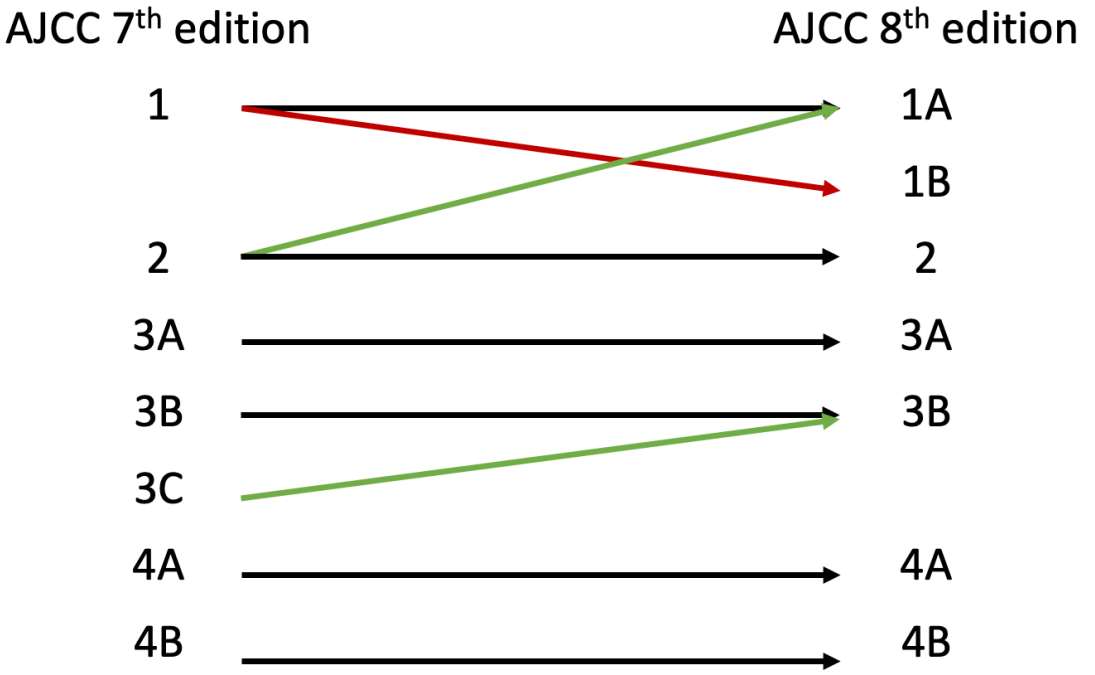
Appendix Figure 1. Liver Cancer Stage Migration



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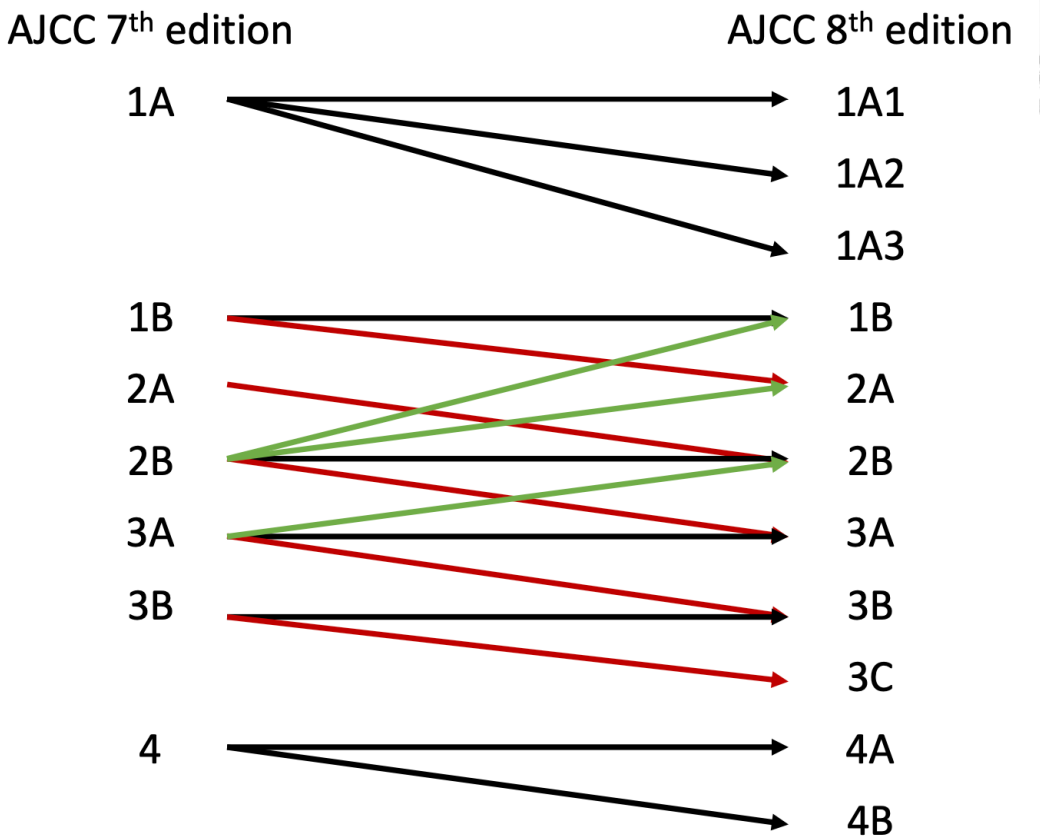
Appendix Figure 2. Lung Cancer Stage Migration



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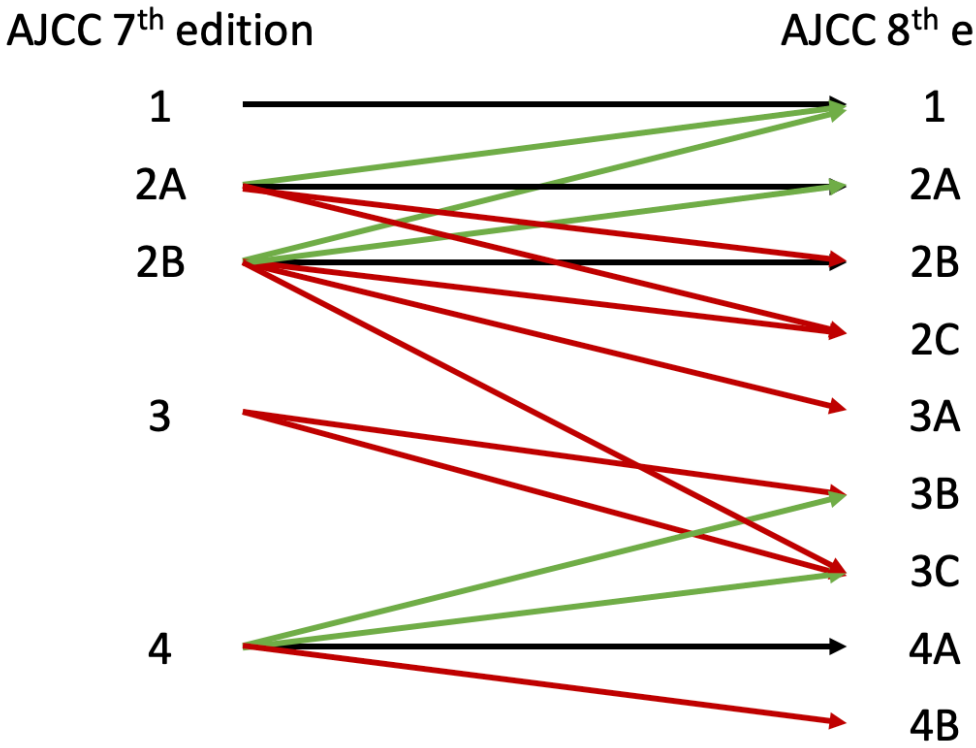
Appendix Figure 3. Prostate Cancer Stage Migration



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