**Modelling of bladder cancer within the Thanzi La Onse Model**

**Background: The Thanzi La Onse Model**

As part of the Thanzi La Onse program a model is being developed which aims to capture the health experiences of the population of Malawi and the consequent interactions with the health care system. The intent is that this model will help to inform future delivery of health care in Malawi. The model is an individual based model – which means we explcitly simulate the individual life and health experiences of a representative proportion of the population of Malawi. The simulation initiates on 1 Jan 2010 and we attempt to simulate the attributes of the population at that point. We can run the model forward to any specified future time point. Each potential intervention and its associated diseases are being modelled. This is being divided into separate disease/intervention modules. This document describes the module on bladder cancer.

**Background: General approach to decisions on modelling causal influences and effects of interventions**

This module was designed in the context of an overall approach to modelling causal effects in general and causal effects of interventions in particular. The overal intent is to adopt as simple a structure as can be conceived, whilst still capturing the essential elements of a disease and the interventions used to prevent or treatment. We include a causal link between a “variable” (by which we mean a characteristic or property of an individual, whether that be demographic, social or biologic), and risk of disease or another variable if there is strong evidence from an overall body of studies that such a causal link exists and is at least moderately strong. In informing such decisions we place particular value on RCTs or studies with a quasi-experimental design such as analyses based on an instrumental variable There is no expectation that such studies will be from Malawi or even from Africa. If there are such local studies and in the unlikely event that they provide strong evidence to suggest that the causal link is substantively different in Malawi then the intent is that this is taken into account and the Malawi-specific link included.

In the special case of a potential causal variable which relates to whether an individual has experienced or is experiencing an intervention the intent is to only include interventions if there is substantial RCT evidence of their beneficial effect, based on trials with objectively ascertained clinical endpoints with low risk of serious bias. Whilst DCP-3 (and to some extent the Malawi EHP) provides an initial list of such interventions and the evidence to support them, where possible our intent has been to form our own opinion on intervention efficacy based on the source trials.

Unless there is evidence to the contrary, the intent is to summarize and incorporate intervention effects into the model as relative risks or rates rather than absolute differences due to the fact that such measures are less likely to differ substantively by context. Interactions between characterstics (on the multiplicative scale) are only to be be incorporated if there is strong evidence. Again, we have not intended to rely on data from Malawi or Africa for such evidence but if local evidence exists which strongly suggests a different effect than elsewhere then the intent is that this modified effect is incorporated in the model.

**Background: Demographic and social characteristics modelled**

Based on data on the distribution of the population in Malawi according to geographic location we assign individuals a geographic location, which maps onto whether they are classified as living in a rural or urban area. Informed largely by data from the Malawi DHS, variables are also created indicating the person’s wealth level (based on 5 quintiles), whether the person has access to improved sanitation, clean drinking water, hand washing facilities, and whether they experience indoor air pollution (wood burning stove). We assign individuals a current education status (none, primary, secondary) which is updated 3 monthly from age 5 to 20. From age 15 we assign BMI in 5 categories, tobacco use status, drinking excess alcohol, having low exercise, high sugar intake, high salt intake, and marital status (never, currently, widowed/divorced). The status with regard to such variables for individuals can change over time. The influences between these variables are described in detail in a separate document.

**Model structure**

**Variables modelled**

The model updates information on each individual with regard to bladder cancer status every 3 months. The model structure is described in Figure 1. Variables that we create for each man aged over 35 in relation to bladder cancer (Table 1) are as follows: bladder cancer status (pc\_status; none, tis\_t1, t2p, metastatic), date of any diagnosis of bladder cancer (pc\_date\_diagnosis), date of any attempted curative treatment (pc\_date\_treatment) and at what stage (pc\_stage\_at\_which\_treatment\_given; no, yes tis\_t1, yes t2p).

**Incidence of Ta/Tis stage bladder cancer**

Table 2 describes the parameters and their values. Jointly, the chosen parameter values produce the model outputs shown in Table 3. Informed by incidence rates of bladder cancer from Malawi cancer registry and other studies (Chasimpha et al, 2017; Parkin et al 2019, Cumberbatch et al 2016), incidence of bladder cancer is assumed to be dependent on age, smoking and infection with schistosomiasis haematobium. The risk per month in non-smokers age < 30 without schistosomiasis haematobium is assumed to be 0.00001 with a 2 fold higher risk in those age 30-49, 3 fold higher risk in those age 50-69 and 3 fold higher thereafter (Chasimpha et al 2017). Current smokers have a 3.5 fold increased risk which reduces to 2.0 fold in ex smokers (Cumberbatch et al 2016), while current “high” schistosomiasis haematobium infection leads to a 5-fold higher risk (Parkin et al 2019).

**Progression between cancer states**

Informed by data on progression of bladder cancer in the absence of treatment (Martini et al 2020, Foresman et al 1997) we assume an annual rate of progression from tis\_t1 to t2+ of 0.05 per month, and from t2+ to metastatic cancer of 0.05 per month. The rate of progression from untreated metastatic cancer to death is 0.05 per month.

**Incidence of blood in urine**

Presentation at late stages of cancer is common in the region (Kingham et al; 2013). In the initial report from the registry for very few cancer cases was their a cancer stage at diagnosis recorded (Msyamboza et al, 2012). We model two main symptoms that lead to the possibility of presentation: blood in urine and pelvic pain. The rate of appearance of blood in urine is assumed to be 0.01 per month at tis\_t1 stage, and this rate increases by 3 times at higher stages, for pelvic pain the rate is 0.0003 in tis\_t1 and 200-fold and 300-fold higher at t2p and metastatic stages.

**Treatment for bladder cancer**

We consider potential medical treatment aimed at cure amongst people who are diagnosed. Depending on stage this might include surgery,chemotherapy and adjuvant treatments. We recognise that availability of treatment is currently extremely limited in Malawi. There were reported in 2015 to be five Malawian oncologists and haematologists involved in full-time cancer care in the whole country (Masamba et al, 2015). There is generally low access to treatments (Kingham et al; 2013).

**Effect of treatment**

Informed by survival in settings with access to curative treatment, the rate ratio for t2+ bladder cancer for people treated with tis\_t1 is estimated as 0.2, while the rate ratio for metastatic bladder cancer in people treated at stage t2+ is 0.3 (<https://www.cancerresearchuk.org/about-cancer/bladder-cancer/survival>).

**Rate of death from bladder cancer**

The death rate from bladder cancer in people with metastatic cancer is assumed to be 0.70 per year.

**Disability weights**

* For persons with any stage of cancer prior to metastatic stage and have never had any treatment, a disability-weight of 0.288 is applied, corresponding to "Diagnosis and primary therapy phase of bladder cancer: Cancer, diagnosis and primary therapy, has pain, nausea, fatigue, weight loss and high anxiety”.
* For persons with any stage of cancer prior to metastatic stage and have ever had any treatment, a disability-weight of 0.049 is applied, corresponding to "Controlled phase of bladder cancer, Generic uncomplicated disease: worry and daily medication, has a chronic disease that requires medication every day and causes some worry but minimal interference with daily activities”
* For persons with a cancer in metastatic stage and with no palliative care, a disability-weight of 0.451 is applied, corresponding to “Metastatic phase of bladder cancer: Cancer, metastatic: has severe pain, extreme fatigue, weight loss and high anxiety."
* For persons with a cancer in metastatic stage and with no palliative care, a disability-weight of 0.451 is applied, corresponding to “Metastatic phase of bladder cancer: Cancer, metastatic: has severe pain, extreme fatigue, weight loss and high anxiety."
* For persons with a cancer in metastatic stage and with palliative care, a disability-weight that is applied that is equal to those with earlier stage cancers without treatment.

**Health System Interactions**

*Care Seeking & Diagnosis*

Blood in urine or pelvic pain are assumed to trigger healthcare seeking to a Non-Emergency Generic Appointment at Facility Level 1, whereupon referral to further health system interaction is indicated. In that appointment, a cytoscopy is undertaken. If that investigation confirms Bladder Cancer and if the stage of cancer is not metastatic then the patient undergoes treatment. If the cancer is confirmed and is in metastatic, the patient is referred to Palliative Care.

We aim for these rates to eventually be informed by data on stage of bladder cancer at diagnosis from the cancer registry, although in the initial report from the registry for very few cancer cases was there a cancer stage at diagnosis recorded (Msyamboza et al, 2012).

*Treatment Initiation & Monitoring*

Treatment is implemented for the patient in a separate single appointment, following diagnosis of any form of stage prior to stage 4 (low/high grade dysplasia and stages 1-3). The patient is monitored every year thereafter, and if the patients has progressed to stage 4, the patient is initiated on Palliative Care.

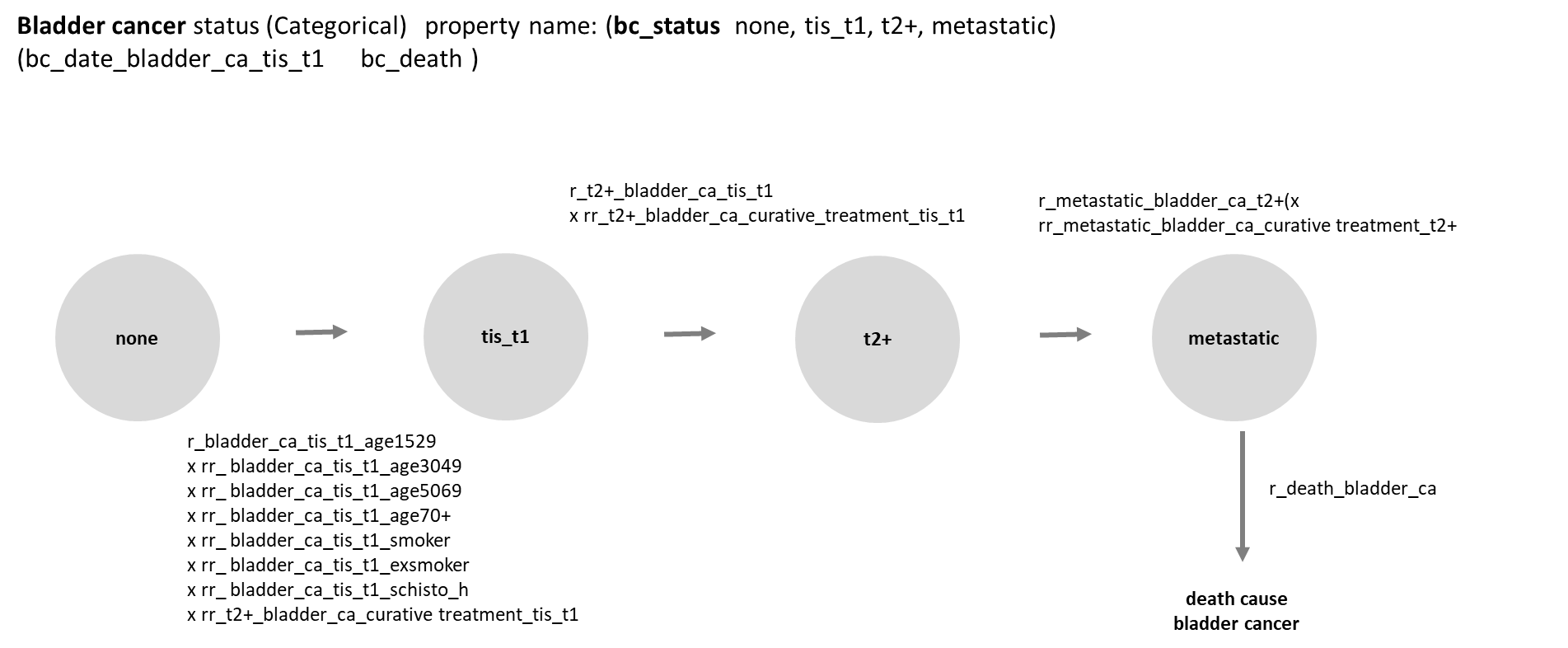
*Palliative Care*

Patients initiated on palliative care remain on palliative care and received a monitoring appointment each month. No benefit for the patient is in effect.

**Main Limitations**

The main limitations are the relative lack of data to directly inform many of the parameter values. Underlying progression of the condition is assumed to follow a similar course as in studies in other parts of the world. For incidence of bladder cancer and rates of diagnosis and availability of curative treatment it is necessary to consider data from Malawi itself given that these are likely to depend on the setting. As it becomes possible to perform more analyses in collaboration with the cancer registry we expect to be able to further inform our parameter values. In future iterations we will consider breaking down attempted curative treatment into surgery, chemotherapy, radiotherapy, and endocrine therapy etc. There is also uncertainty over disability weights.

**Figure 1. Bladder cancer status**



**Table 1. Properties modelled.**

|  |  |
| --- | --- |
| **Variable** | **Description** |
| bc\_status | none, tis\_t1, metastatic |
| bc\_date\_diagnosis | date diagnosis |
| bc\_stage\_at\_which\_treatment\_given | received attempted curative treatment (never, yes tis\_t1, yes t2p) |
| bc\_date\_treatment | date attempted curative treatment for bladder cancer |
| bc\_date\_palliative\_care | date start palliative care (note this is not bladder cancer-specific) |

|  |  |  |  |
| --- | --- | --- | --- |
| **Table 2. Description of parameters and proposed values** (rates are expressed per 1 month) | | | |
| **Parameter** | **Proposed value** | **Description** | **Notes** |
| r\_bladder\_ca\_tis\_t1\_age1529 | **0.00001** | annual rate of incident tis\_t1 bladder cancer for non smokers age 15-29 without schisto h | Indirectly informed by Chasimpha et al 2017 |
| rr\_ bladder\_ca\_tis\_t1\_age3049 | **2** | rate ratio for incident tis\_t1 bladder cancer for people age 30-49 | Chasimpha et al 2017 |
| rr\_ bladder\_ca\_tis\_t1\_age5069 | **3** | rate ratio for incident tis\_t1 bladder cancer for people age 50-69 | Chasimpha et al 2017 |
| rr\_ bladder\_ca\_tis\_t1\_age70+ | **3** | rate ratio for incident tis\_t1 bladder cancer for people age 70+ | Chasimpha et al 2017 |
| rr\_ bladder\_ca\_tis\_t1\_smoker | **3.5** | rate ratio for incident tis\_t1 bladder cancer for current smoker | Cumberbatch et al 2016 |
| rr\_ bladder\_ca\_tis\_t1\_exsmoker | **2.0** | rate ratio for incident tis\_t1 bladder cancer for ex smoker | Cumberbatch et al 2016 |
| rr\_ bladder\_ca\_tis\_t1\_schisto\_h | **5** | rate ratio for incident tis\_t1 bladder cancer if high schisto h |  |
| r\_t2+\_bladder\_ca\_tis\_t1 | **0.15** | rate of progression to t2+ bladder cancer from tis\_t1 | Martini et al 2020, Foresman et al 1997 |
| rr\_t2+\_bladder\_ca\_curative\_treatment\_tis\_t1 | **0.10** | rate ratio for progression to t2+ bladder cancer if had attempted curative treatment at tis\_t1 |  |
| r\_metastatic\_bladder\_ca\_t2+ | **0.15** | annual rate of progression to metastatic bladder cancer if at stage t2+ |  |
| rr\_metastatic\_bladder\_ca\_curative treatment\_t2+ | **0.20** | rate ratio for progression to metastatic bladder cancer if had attempted curative treatment at t2+ |  |
| r\_death\_bladder\_ca | **0.2** | annual rate of death in people with metastatic bladder cancer |  |

**Table 3. Model outputs and observed data from Malawi**

(note this is with treatment given in 100% of diagnosed people pre-metastatic)

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Model Output** | **Observed Data** | **Notes** |
| Number of incident diagnoses of bladder cancer per year | ~800 | 708 | Globocan\* |
| Rate of diagnosed bladder cases  (/100,000 aged > 15 per year) | 9.7  (in 2020) | 4.0 (equal by gender) | During 2008 – 2010, Blantyre. Chasimpha et al. 2017. |
| Number of people living with bladder cancer (any stage from tis\_t1) in 2020, whether diagnosed or not | ~4000 | Not available by definition |  |
| Number of people living with **diagnosed** bladder cancer (any stage from tis\_t1) in 2020, whether diagnosed or not | ~1500 | No data identified data so far to inform. | 1235 (5 year prevalence) Globocan\* |
| Percentage of incident bladder cancer cases diagnosed tis\_t1 | ~20% | No data identified data so far to inform. |  |
| Number of people given attempted curative treatment for bladder cancer per year | 300 | Low but have not identified data so far. |  |
| Number of deaths from bladder cancer per year (modelled output includes people never diagnosed) | ~600 | 396 | Globocan\* |

\* Globocan Methods: Incidence Country-specific data source: National Cancer Registry of Malawi Method: Most recent rates from a single registry applied to 2018 population Mortality Country-specific data source: No data Method: Estimated from national incidence estimates by modelling, using incidence:mortality ratios derived from cancer registry data in neighbouring countries Prevalence Computed using sex-; site- and age-specific incidence to 1-;3- and 5-year prevalence ratios from Nordic countries for the period (2000-2009), and scaled using Human Development Index (HDI) ratios

**References**

Riffenburgh et al. Survival Patterns of Cancer Patients. Cancer 2001; 91:2469–75.

https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/

Msyamboza et al. BMC Research Notes 2012, 5:149 http://www.biomedcentral.com/1756-0500/5/149

Moses et al. Risk factors for common cancers among patients at Kamuzu Central Hospital in Lilongwe, Malawi: A retrospective cohort study. Malawi Medical Journal 29 (2): June 2017

Chasimpha et al. Three-year cancer incidence in Blantyre, Malawi (2008–2010). Int. J. Cancer: 141, 694–700 (2017).

Masamba et al. The state of oncology in Malawi in 2015. Malawi Medical Journal; 27(3): 77-78 September 2015.

Msyamboza et al. Burden of cancer in Malawi; common types, incidence and trends: National population-based cancer registry. BMC Research Notes 2012, 5:149

Mukhula et al. Characterising cancer burden and quality of care at two palliative care clinics in Malawi. Malawi Medical Journal 29 (2): June 2017

Gowshall et al. The increasing prevalence of non-communicable diseases in low-middle income countries: the view from Malawi. International Journal of General Medicine 2018:11 255–264

Malawi DHS 2010, 2015/16 <https://dhsprogram.com/>

Salomon et al. Common values in assessing health outcomes from disease and injury: disability weights measurement study for the Global Burden of Disease Study 2010. Lancet 2012; 380: 2129–43. <http://www.biomedcentral.com/1756-0500/5/149>

Malawi Cancer Consortium <http://malawicancerconsortium.web.unc.edu/>

Stefan et al. Cancer Care in Africa: An Overview of Resources Volume 1, Issue 1, October 2015.. J Glob Oncol 1:30-36. © 2015 by American Society of Clinical Oncology.

Globocan <http://gco.iarc.fr/today/data/factsheets/populations/454-malawi-fact-sheets.pdf>

Parkin M, Hämmer L, Ferlay J, Kantelhardt EJ. Cancer in Africa 2018: The role of infections. Int. J. Cancer 2019

van der Werf MJ et al. Quantification of clinical morbidity associated with schistosome infection in sub-Saharan Africa. Acta Tropica 86 (2003) 125\_/139

Rambau et al. Infectious Agents and Cancer 2013, 8:19 Schistosomiasis and urinary bladder cancer in North Western Tanzania: a retrospective review of 185 patients <http://www.infectagentscancer.com/content/8/1/19>

Tadao Kakizoe, Lorelei A. Mucci, Peter C. Albertsen & Michael J. Droller

(2008) Screening for bladder cancer: Theoretical and practical issues in considering the treated and

untreated natural history of the various forms of the disease, Scandinavian Journal of Urology and

Nephrology, 42:sup218, 191-212, DOI: 10.1080/03008880802284936

Foresman et al. Bladder Cancer: Natural History, Tumor Markers, and Early Detection Strategies. Seminars in Surgical Oncology 1997; 13:299–306

Martini et al. The natural history of untreated muscle-invasive bladder cancer. BJU Int 2020; 125: 270–275.

E. De Berardinis et al. T1G3 high-risk NMIBC (non-muscle invasive bladder cancer): conservative treatment versus immediate cystectomy. Int Urol Nephrol (2011) 43:1047–1057

Parkin M et al. Part I: Cancer in Indigenous Africans—burden, distribution, and trends. Lancet Oncol 2008; 9: 683–92

Carla Carrilho et al. Cancer incidence in Mozambique in 2015–2016: data from the Maputo Central Hospital Cancer Registry. European Journal of Cancer Prevention 2019, 28:373–376

P Mtonga et al . Biopsy case mix and diagnostic yield at a Malawian central hospital. Malawi Medical Journal; 23(3): 62-64 September 2013

Antoni S et al. Bladder Cancer Incidence and Mortality: A Global Overview and Recent Trends. DOI: 10.1016/j.eururo.2016.06.010 European urology , 2017, Vol.71(1), p.96-108

Cumberbatch MG et al. The Role of Tobacco Smoke in Bladder and Kidney Carcinogenesis: A Comparison of Exposures and Meta-analysis of Incidence and Mortality Risks. DOI: 10.1016/j.eururo.2015.06.042 European urology , 2016, Vol.70(3), p.458-466

Kingham TP et al. Treatment of cancer in sub-Saharan Africa. Lancet Oncol 2013; 14: e158–67

Gopal S, Krysiak R, Liomba NG, Horner M-J, Shores CG, et al. (2013) Early Experience after Developing a Pathology Laboratory in Malawi, with Emphasis on Cancer Diagnoses. PLoS ONE 8(8): e70361. doi:10.1371/journal.pone.0070361

Parkin DM et al. Cancer in Sub-Saharan Africa. International Agency for Research on Cancer Lyon, France 2018