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## Treatment patterns and survival analysis in 9014 patients with malignant pleural mesothelioma from Belgium, the Netherlands and England

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### ABSTRACT

**Introduction:** Pleural mesothelioma has a dismal prognosis and is refractory to local treatment. Combination chemotherapy can increase median survival by several months and was gradually introduced in the period 2003–2006. Elderly patients may be unfit for chemotherapy but little is known about age-related treatment practice. To determine treatment patterns and current survival outcome, three large population-based registries were queried in a uniform manner.

**Methods:** Data from the Belgian Cancer Registry, the Netherlands Cancer Registry and the UK National Lung Cancer Audit were analyzed for patients diagnosed with pleural mesothelioma since 2007. Treatment patterns and survival rates were compared between countries and age-groups.

**Results:** The study included 900, 2306 and 5808 patients from Belgium, the Netherlands and England, respectively. Fifty-nine percent of patients were 70 years or older and 84% were men. Chemotherapy use decreased with advancing age and was used more often in Belgium (60%) than in the Netherlands (41%) and England (37%). For patients aged 70–79 years, chemotherapy use was 55%, 36% and 34% in the respective countries. Median survival was 10.7 months in Belgium versus 9.2 months for the Netherlands and 9.5 months for England. Survival rates decreased with advancing age. On average, median survival was 5.6 months longer for patients treated with chemotherapy, irrespective of age.

**Conclusions:** Combined analysis of data from three countries with high mesothelioma rates demonstrates that chemotherapy has become standard treatment for younger patients. Elderly patients currently account for more than half of all cases and less toxic treatment options will be required to improve their prospects.

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### 1. Introduction

Malignant pleural mesothelioma (MPM) is known for its causal association with asbestos exposure and its dismal prognosis. Malignant mesothelioma used to be a rare disease but high incidence rates can be found in industrial regions within Belgium, the Netherlands and the United Kingdom (UK). For men, the

age-standardized incidence rates (European population standard) peaked in Belgium in 2004 (34/million), in the Netherlands in 2005 (51/million) and in the UK in 2006 (55/million).

Pleural mesothelioma has long been considered refractory to treatment until novel chemotherapy regimens were proven effective in two randomized trials [1,2]. Combination chemotherapy was gradually introduced in the period 2003–2006 and median survival improved at a population-based level [3,4].

In the western world, the mesothelioma population is ageing quickly as a result of demographic trends and historical asbestos exposure patterns. Survival rates decrease with advancing age [5]

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and elderly patients may be unfit to receive chemotherapy. An Italian study [6] compared results with pemetrexed-carboplatin in patients aged <70 and  $\geq$ 70 years. Median age was 65 years and 27% of patients was  $\geq$ 70 years old. Disease control was comparable (67% vs. 60%) but hematological toxicity was more frequent among elderly patients (anemia 7% vs. 21%). The European guideline for the management of MPM [7] does not endorse specific approaches for the elderly but acknowledges the WHO performance score as an influential factor. Little is known about age-specific treatment patterns in the general population while elderly patients are underrepresented in clinical trials. Median age in the cisplatin-pemetrexed trial [1] was 61 years versus 58 years in the cisplatin-raltitrexed trial [2]. To explore the impact of age on chemotherapy use and survival, we analyzed individual databases from three European countries.

## 2. Methods

Three independent national registries were queried regarding patients with malignant pleural mesothelioma (ICD-O C38.4, morphology 9050–9053). Only records with diagnosis after 2006 were included to ensure that modern chemotherapy regimens were available. Patients were included from 2007 through 2010 for Belgium, and from 2007 through 2011 for the Netherlands and England. To allow comparison with clinical series, the study was restricted to patients with pathological verification of the diagnosis (cytology or histology). Date of diagnosis is based on the date of the pathology report.

Cancer incidence data from the nationwide Belgian Cancer Registry (BCR), founded in 2005, completely cover Belgium from 2004 onwards [8]. Data flow to the BCR relies on information from the oncological care programs (clinical network) and from pathology laboratories (pathological network). Vital status is retrieved from the “Kruispuntbank van de Sociale Zekerheid/Banque Carrefour de la Sécurité Sociale”. Treatment data are based on administrative data obtained from the Belgian health insurance companies by the Intermutualistic Agency (IMA/AIM). These data contain information on the reimbursed cancer-related diagnostic and therapeutic procedures and pharmaceuticals. Data on treatment reported at the time of the multidisciplinary oncological consultation serve as an additional quality control. Because the administrative health insurance data do not directly refer to a specific diagnosis, timeframes around the date of diagnosis are used to define relevant treatments. Surgery includes both pneumonectomy and pleural resection, performed up to 9 months after diagnosis. The term pleural resection may have been misused for large biopsies. Radiotherapy includes both long series (more than 10 fractions) and short series for palliative, prophylactic or adjuvant indications. Chemotherapy information is recorded by type of agent, allowing detailed specification of treatment regimens. A detailed description of surgical nomenclature codes and the timeframes used to define surgery, radiotherapy and chemotherapy is provided in Appendix 1a (Supplementary File).

The nationwide Netherlands Cancer Registry is based on notification by pathology departments and hospital discharge records. Population-based coverage was achieved in 1989. Information on patient, tumor and treatment characteristics is collected by trained data clerks. Vital status is retrieved from automated linkage with the national civil registry. Only the initial treatment is recorded, so excluding later treatment after expectant management or disease progression. Surgery is coded for any type of resection of the primary tumor and may comprise varying procedures such as extrapleural pneumonectomy, pleurectomy, decortication or wedge resections. Radiotherapy is coded for irradiation of the primary tumor, so excluding radiation of intervention sites or distant metastases.

The UK National Lung Cancer Audit (NLCA) was established in 2004 and comprises data on patients with lung cancer or pleural mesothelioma [9]. Data is retrieved via the multidisciplinary teams at National Health Service (NHS) hospitals. The database currently consists of over 225,000 patients, including 5% with mesothelioma [10]. Population coverage for mesothelioma is estimated at 85% and 76% of mesothelioma diagnoses are pathologically verified. For this study, we restricted the analyses to NLCA patients from England. Vital status is retrieved from the Patient Demographics Service. The NLCA database was linked with the inpatient Hospital Episode Statistics (HES) database to identify Office of Population Censuses and Survey Classification of Intervention (OPCS-4) codes for procedures consistent with potentially curative surgery (excluding pleurodesis) and procurement of chemotherapy (see Appendix 1b and 1c, Supplementary File). The NLCA was used to identify patients who had received chemotherapy as an out-patient. Radiotherapy is recorded in the NLCA, but it is not possible to differentiate the use of this modality for curative or palliative intent, and it may include the use of prophylactic radiotherapy to intervention sites.

Patients in whom the date of diagnosis was equal to the date of death were excluded from the analysis. Information regarding stage at diagnosis was ignored because the current clinical TNM stage is considered inaccurate [11]. Type of chemotherapy was only documented in Belgium. However, platinum-pemetrexed is the presumed standard regimen for the other two countries. Treatment timeframes clearly differ between the three registries. For the Netherlands, only the initial treatment is recorded, i.e. according to the primary treatment plan at diagnosis. For Belgium, surgical treatment is taken into account up to 9 months after diagnosis and may include treatment that was initiated after progression. For England, treatment information relied on NLCA-HES linked records, which may include several years after diagnosis.

Results were independently analyzed for the three individual registries (HDS, RD, AK) according to a uniform protocol. Records were tabulated by age, gender and treatment category. Additional results are reported regarding specific information that was available for individual registries. Median survival, including interquartile range (25 to 75 percentile), was calculated from the day of histopathological diagnosis, stratifying for age and treatment with chemotherapy. Given the descriptive nature of the study and the large number of patients involved, we refrained from any formal statistical analysis, as even minor differences will produce statistical significance in large subgroups.

## 3. Results

This series included 900 patients from Belgium, 2306 patients from the Netherlands and 5808 patients from England (Table 1). Patients were mainly men (84%) and 59% was 70 years or older. Age and gender distributions were comparable for the three countries. Chemotherapy was used more often in Belgium (60%) than in the Netherlands (41%) and England (37%). Radiotherapy was least often recorded in the Netherlands (10%). In Belgium, radiotherapy involved short series in 81% of patients treated. Surgery (16%) and the combination of surgery and chemotherapy (11%) were more frequently used in Belgium. For the Belgian series, surgery comprised pneumonectomy in 6.1% of patients and pleurectomy in 10.2%. Chemotherapy consisted of a pemetrexed containing regimen in 90% of Belgian patients.

The use of chemotherapy decreased with increasing age for all three countries (Table 2). More than half of the patients aged below 70 years received chemotherapy, while chemotherapy rates were considerably higher in Belgium. In patients aged 70–79 years, chemotherapy was administered in 55%, 36% and 34% in Belgium,

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