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Pancreatic Cancer and Hospital Management in Portugal: An Epidemiological View

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1. Theoretical Framework – Background

The incidence of pancreatic cancer is increasing worldwide with a greater than 2-fold increase observed in the last 30 years [1] (see Charts 1 and 2 in the Appendix). It is the third leading cause of death from malignant tumors in the United States [2] and the fourth in Europe [3, 4].

Pancreatic cancer can originate from endocrine or exocrine pancreatic cells. The most common pancreatic cancers are those from exocrine origin, such as pancreatic adenocarcinoma, which are extremely aggressive and potentially lethal [5, 6]. The mortality rates related to these types of tumors have increased substantially, including in Portugal, with a 2-fold increase over 25 years (from 1991 to 2015), which reflects an annual increase of approximately 3% [5].

According to the World Pancreatic Cancer Coalition, approximately 1,300 new cases of pancreatic cancer are diagnosed every year in Portugal. Upon diagnosis, curative treatments (adenocarcinomas) cannot be offered for most patients. Nevertheless, an increase in the incidence of pancreatic tumors which can be managed with curative treatments – namely neuroendocrine tumors and pancreatic cystic neoplasms – has been observed [5].

That said, it is essential that awareness campaigns aimed to educating the population about the characteristics of pancreatic cancer be encouraged. By promoting early diagnosis through the identification of warning signs and raising awareness on preventive measures and risk factors, the access to reference centers may be increased, resulting in short- and long-term cost reductions [7], and increases in long-term survival [5].

Regarding cancer, the National Health Plan in Portugal aims to decrease the number of cases of preventable cancers and diagnostic delays by focusing on prevention and early diagnosis measures; it also aims to reduce the burden of the disease on the patients and their families, as well as ensure equal and accessible treatment to all citizens. One of the goals of the National Health Plan is to ensure that 75% of all pancreatic cancers are treated in reference centers [8].

2. Epidemiologic Characteristics

Adenocarcinoma (exocrine pancreatic cancer) is the most common pancreatic cancer (95% of all cases) [9].

Pancreatic cancer has the lowest survival rate among all cancers in Europe and is the third most common digestive system neoplasm in Portugal, behind colon and stomach cancer; also, it is the seventh leading cause of death from malignant tumors (Table 1 – Appendix). It has a higher prevalence in men (Table 2 – Appendix), and overall mortality is higher at ages 75-79 (Table 3 – Appendix). However, the number of deaths at earlier ages seems to be increasing.

Currently, the mean 5-year survival rate is of 3% to 9%. Life expectancy upon diagnosis is of 4.6 months, and the number of deaths due to pancreatic cancer has almost doubled in the last three decades. In a recent study conducted in Portugal, a 2-fold increase on the number of deaths from pancreatic cancer over the last 25 years has been observed – i.e., more than 1,500 deaths per year in 2017 [10, 11, 12].

According to current data from the National Institute of Statistics (INE, 2019), the number of deaths from pancreatic cancer is ap-

parently higher in the Metropolitan Area of Lisbon, followed by the North and Central parts of the country (Table 4 – Appendix). However, these data need to be further evaluated.

There seems to be a trend toward progressive increases in deaths from pancreatic cancer as well as an increase in prevalence in men, according to an evaluation conducted by INE on deaths occurred between 1990 and 2019 (Table 5 – Appendix) [13, 14].

It is estimated that two thirds of the most common risk factors associated with pancreatic cancer are potentially modifiable, which represents an opportunity for disease prevention. These are: chronic smoking (75% higher risk compared to non-smokers), obesity

(47% higher risk compared to individuals with BMI within the normal range), diabetes mellitus (50% higher risk for individuals older than 50 years of age and who have been diagnosed with diabetes for less than four years compared with those who have been diagnosed with diabetes over 5 years); chronic pancreatitis (4% of the patients will develop pancreatic cancer); familial predisposition (higher risk for individuals with two first-degree relatives affected or 3 relatives diagnosed with the disease being at least one of them a first-degree relative or presenting with hereditary genetic syndromes, such as Peutz-Jeghers syndrome). Studies indicate that 5% to 10% of all cases of pancreatic cancer are related to genetic conditions [15].

Table 1: Deaths by geographic distribution of residence (NUTS I/II/III) and gender, according to the cause of death (ICD-10 - European short list). Data obtained from the Death Certificate Information System available until February 17, 2020. Source: INE

| Distribuicao geografica de residenciae sexo | | LES - 07 Tumores malignos | LES - 08 Tumor malingo do labio, cavidade bucal e faringe | | LES - 10 Tumor maligno do estomago | LES - 11 Tumor maligo do colon | LES - 12 Tumor maligno do reto e anus | LES - 13 Tumor maligno do figado e das vias blreas intra- hepaticas | LES - 14 Tumor maligno do pancreas | LES - 15 Tumor maligno da laringe e traqueia/ bronquios/ pulmao | LES - 16 Tumor maligno da pele | LES - 17 Tumor maligno da mama | LES - 18 Tumor maligno do colo do utero | LES - 19 Tumor maligno de outras partes do utero | LES - 20 Tumor maligno do ovario | LES - 21 Tumor maligno da prostata | LES - 22 Tumor maligno do rim | LES - 23 Tumor maligno da bexiga | LES - 24 Tumor maligno do tecido infatico/ hemato poetico |
|--|----|------------------------------------|---|-----|---|---|--|---|---|---|--|--|--|--|---|---|---|---|---|
| | HM | 28,544 | 829 | 552 | 2,249 | 2,624 | 1,205 | 1,266 | 1,653 | 4,717 | 265 | 1,909 | 221 | 494 | 391 | 1,903 | 454 | 867 | 2,453 |
| Total | Н | 16,865 | 682 | 477 | 1,367 | 1,477 | 744 | 928 | 894 | 3,569 | 144 | 29 | // | // | // | 1,903 | 296 | 652 | 1,347 |
| | M | 11,679 | 147 | 75 | 882 | 1,147 | 461 | 338 | 759 | 1,148 | 121 | 1,880 | 221 | 494 | 391 | // | 158 | 215 | 1,106 |
| | HM | 28,464 | 826 | 548 | 2,246 | 2,620 | 1,204 | 1,261 | 1,649 | 4,703 | 264 | 1,902 | 221 | 494 | 391 | 1,901 | 454 | 865 | 2,439 |
| portugal | Н | 16,815 | 680 | 474 | 1,366 | 1,474 | 743 | 926 | 892 | 3,557 | 143 | 29 | // | // | // | 1,901 | 296 | 650 | 1,336 |
| | M | 11,649 | 146 | 74 | 880 | 1,146 | 461 | 335 | 757 | 1,146 | 121 | 1,873 | 221 | 494 | 391 | // | 158 | 215 | 1,103 |
| | HM | 27,188 | 777 | 518 | 2,167 | 2,551 | 1,151 | 1,208 | 1,583 | 4,462 | 252 | 1,803 | 206 | 467 | 375 | 1,835 | 441 | 825 | 2,330 |
| Continente | Н | 16,085 | 636 | 451 | 1,320 | 1,442 | 706 | 891 | 851 | 3,369 | 136 | 28 | // | // | // | 1,835 | 287 | 618 | 1,281 |
| | M | 11,103 | 141 | 67 | 847 | 1,109 | 445 | 317 | 722 | 1,093 | 116 | 1,775 | 206 | 467 | 375 | // | 154 | 207 | 1,049 |

Table 2: Deaths by nature (ICD-10 - European short list) and gender, according to the month of death. Data obtained based on information from the Death Certificate Information System available until February 17, 2020. Source: INE

| Causa de morte e sexo | | Total | janeiro | Fevereiro | Marco | Abril | Maio | Junho | Julho | Agosto | Setembro | Outubro | Novembro | Dezembro |
|---|----|-------|---------|-----------|-------|-------|------|-------|-------|--------|----------|---------|----------|----------|
| | НМ | 1,205 | 101 | 89 | 100 | 103 | 91 | 93 | 119 | 106 | 87 | 112 | 110 | 94 |
| LES - 12 Tumor maligno de reto e anus | Н | 744 | 67 | 55 | 61 | 60 | 55 | 59 | 72 | 60 | 57 | 67 | 69 | 62 |
| ue rete e unus | M | 461 | 34 | 34 | 39 | 43 | 36 | 34 | 47 | 46 | 30 | 45 | 41 | 32 |
| LES - 13 | НМ | 1,266 | 115 | 105 | 109 | 91 | 107 | 101 | 109 | 105 | 105 | 114 | 92 | 113 |
| Tumor maligno | Н | 928 | 92 | 78 | 88 | 63 | 77 | 75 | 83 | 71 | 80 | 80 | 69 | 72 |
| do figado e das vias billiares intrahepaticas | M | 338 | 23 | 27 | 21 | 28 | 30 | 26 | 26 | 34 | 25 | 34 | 23 | 41 |
| | НМ | 1,653 | 146 | 125 | 137 | 124 | 127 | 137 | 148 | 124 | 169 | 142 | 128 | 146 |
| LES - 14 Tumor maligno do pancreas | Н | 894 | 82 | 64 | 71 | 68 | 67 | 73 | 80 | 67 | 96 | 91 | 63 | 72 |
| uo panereas | M | 759 | 64 | 61 | 66 | 56 | 60 | 64 | 68 | 57 | 73 | 51 | 65 | 74 |
| LES - 15 Tumor maligno | НМ | 4,717 | 425 | 360 | 399 | 374 | 375 | 394 | 368 | 429 | 370 | 411 | 408 | 404 |
| da larginge e traqueia/ | Н | 3,569 | 321 | 269 | 307 | 272 | 294 | 289 | 290 | 320 | 281 | 305 | 313 | 308 |
| bronquios/ pulmao | M | 1,148 | 104 | 91 | 92 | 102 | 81 | 105 | 78 | 109 | 89 | 106 | 95 | 96 |
| | НМ | 265 | 22 | 24 | 30 | 18 | 22 | 22 | 20 | 22 | 20 | 22 | 21 | 22 |
| LES - 16 Tumor maligno da pele | Н | 144 | 10 | 12 | 17 | 5 | 13 | 11 | 15 | 10 | 12 | 15 | 11 | 13 |
| au pere | M | 121 | 12 | 12 | 13 | 13 | 9 | 11 | 5 | 12 | 8 | 7 | 10 | 9 |
| Les - 17 Tumor maligno | НМ | 1,909 | 171 | 160 | 158 | 149 | 178 | 157 | 155 | 146 | 160 | 139 | 158 | 167 |
| da mama | Н | 29 | 5 | 4 | 1 | 5 | 0 | 2 | 2 | 1 | 5 | 2 | 1 | 1 |

Table 3: Deaths by nature (ICD-10 - European short list) and gender, according to age group. Data obtained based on information from the Death Certificate Information System available until February 17, 2020. Source: INE

| | | | | | | | | | | 0 | a 64 | | | | | | | | | | 65 | e + | | |
|---------------------------------------|----|-------|-------|-------|---|-----|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-------|-----------|-----------|-----------|-----------|------|-----|
| Causa de morte e sexo | | Total | Total | 0-4 | | 5-9 | 10- 14 | 15- 19 | 20- 24 | 25- 29 | 30- 34 | 35- 39 | 40- 44 | 45- 49 | 50- 54 | 55- 59 | 60- 64 | Total | 65- 69 | 70- 74 | 75- 79 | 80- 84 | 85e+ | |
| | | | | Total | 0 | 1-4 | | | | | | | | | | | | | | | | | | |
| | НМ | 2,642 | 446 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 5 | 10 | 26 | 46 | 79 | 101 | 178 | 2178 | 244 | 320 | 372 | 511 | 731 |
| LES - 11 Tumor maligno do colon | Н | 1477 | 256 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 12 | 25 | 45 | 57 | 116 | 1224 | 153 | 189 | 228 | 306 | 345 |
| | M | 1147 | 190 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 4 | 10 | 14 | 21 | 34 | 44 | 62 | 957 | 91 | 131 | 144 | 205 | 386 |
| | НМ | 1205 | 262 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 3 | 3 | 13 | 30 | 43 | 78 | 89 | 943 | 129 | 147 | 142 | 242 | 283 |
| LES - 12 Tumor maligno de reto e anus | Н | 744 | 171 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 1 | 1 | 9 | 19 | 29 | 50 | 60 | 573 | 90 | 95 | 92 | 142 | 154 |
| | M | 461 | 91 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 2 | 2 | 4 | 11 | 14 | 28 | 29 | 370 | 39 | 52 | 50 | 100 | 129 |
| LES - 13 Tumor maligno | НМ | 1266 | 367 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 2 | 3 | 2 | 11 | 22 | 54 | 110 | 161 | 899 | 161 | 209 | 181 | 176 | 172 |
| do figado e das vias | Н | 928 | 303 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 2 | 0 | 1 | 8 | 19 | 47 | 94 | 131 | 625 | 132 | 159 | 133 | 108 | 93 |
| biliares intra-hepaticas | M | 338 | 64 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 3 | 1 | 3 | 3 | 7 | 16 | 30 | 274 | 29 | 50 | 48 | 68 | 79 |
| | НМ | 1653 | 328 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 2 | 4 | 8 | 25 | 55 | 101 | 132 | 1325 | 193 | 270 | 280 | 274 | 308 |
| LES - 14 Tumor maligno do pancreas | Н | 894 | 212 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 2 | 6 | 19 | 37 | 66 | 80 | 682 | 123 | 155 | 147 | 134 | 123 |
| | M | 759 | 116 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 2 | 2 | 6 | 18 | 35 | 52 | 643 | 70 | 115 | 133 | 140 | 185 |
| LES - 15 Tumor maligno | HM | 4717 | 1507 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 2 | 17 | 53 | 123 | 254 | 420 | 636 | 3210 | 718 | 761 | 635 | 575 | 521 |
| da laringe e traqueia/ | Н | 3569 | 1145 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 12 | 39 | 81 | 185 | 325 | 501 | 2424 | 572 | 601 | 479 | 431 | 341 |
| bronquios/pulmao | M | 1148 | 362 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 5 | 14 | 42 | 69 | 95 | 135 | 786 | 146 | 160 | 156 | 144 | 180 |
| LEG 16T E | НМ | 265 | 83 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 3 | 5 | 6 | 12 | 16 | 16 | 24 | 182 | 34 | 37 | 26 | 34 | 51 |
| LES - 16 Tumor maligno da pele | Н | 144 | 46 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 3 | 3 | 6 | 8 | 5 | 19 | 98 | 14 | 25 | 15 | 18 | 26 |
| _ | M | 121 | 37 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 2 | 3 | 6 | 8 | 11 | 5 | 84 | 20 | 12 | 11 | 16 | 25 |
| LES -17 Tumor maligno | НМ | 1909 | 634 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 18 | 37 | 72 | 100 | 108 | 159 | 139 | 1275 | 151 | 184 | 184 | 264 | 492 |
| da mama | Н | 29 | 4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | 25 | 2 | 3 | 6 | 8 | 6 |

Table 4: Deaths by Causes of Death, data obtained based on information from the Death Certificate Information System available until February 17, 2020. Source: INE

| Distribuicao geografica de residencia e sexo | | LES-07 Tumores malignos | LES-08 Tumor maligno do labio, cavidade bucal e faringe | LES-09 Tumor maligno do esofago | l do | LES-11 Tumor maligno do colon | LES-12 Tumor maligno do reto e anus | LES-13 Tumor maligno do figade e das vias biliares intra- hepaticas | | LES-15 Tumor maligno da laringe e traqueia/ bronquios | LES-16 Tumor malingo da pele | LES-17 Tumor malingo da mama | LES-18 Tumor malingo do colo do utero | LES-19 Tumor malingo de outras partes do utero | LES-20 Tumor malingo do ovario | LES-21 Tumor malingo da prostata | LES-22 Tumor malingo do rim | LES- 23 Tumor malingo da bexiga | LES-24 Tumor malingo do tecido linfatico/ hematopo etico |
|--|----|-------------------------------|---|---|------|--|---|--|-----|--|---------------------------------------|--|---|--|--|--|--------------------------------------|---|--|
| | НМ | 9,091 | 288 | 202 | 921 | 805 | 334 | 415 | 483 | 1698 | 72 | 523 | 60 | 134 | 111 | 551 | 146 | 267 | 706 |
| Norte | Н | 5491 | 232 | 173 | 556 | 445 | 189 | 303 | 267 | 1304 | 37 | 8 | // | // | // | 551 | 92 | 188 | 391 |
| | M | 3600 | 56 | 29 | 365 | 360 | 145 | 112 | 216 | 394 | 35 | 515 | 60 | 134 | 111 | // | 54 | 79 | 315 |
| | HM | 6689 | 181 | 122 | 472 | 664 | 312 | 308 | 402 | 901 | 55 | 466 | 38 | 109 | 92 | 535 | 96 | 211 | 588 |
| Centro | Н | 3897 | 146 | 113 | 282 | 378 | 194 | 237 | 202 | 670 | 31 | 5 | // | // | // | 535 | 63 | 150 | 335 |
| | M | 2792 | 35 | 9 | 190 | 286 | 118 | 71 | 200 | 231 | 24 | 461 | 38 | 109 | 92 | // | 33 | 61 | 253 |
| A.M. | HM | 7817 | 218 | 141 | 542 | 723 | 308 | 365 | 500 | 1306 | 81 | 574 | 75 | 154 | 115 | 480 | 128 | 225 | 716 |
| Lisboa | Н | 4514 | 183 | 117 | 326 | 404 | 194 | 264 | 278 | 964 | 49 | 9 | // | // | // | 480 | 82 | 177 | 371 |
| Lisuua | M | 3303 | 35 | 24 | 216 | 319 | 114 | 101 | 222 | 342 | 32 | 565 | 75 | 154 | 115 | // | 46 | 48 | 345 |
| | HM | 2312 | 60 | 24 | 163 | 254 | 131 | 83 | 123 | 327 | 19 | 148 | 20 | 52 | 41 | 170 | 46 | 76 | 210 |
| Alentejo | Н | 1384 | 49 | 21 | 108 | 150 | 86 | 58 | 75 | 254 | 7 | 3 | // | // | // | 170 | 29 | 63 | 117 |
| | M | 928 | 11 | 3 | 55 | 104 | 45 | 25 | 48 | 73 | 12 | 145 | 20 | 52 | 41 | // | 17 | 13 | 93 |
| | HM | 1279 | 30 | 29 | 69 | 105 | 66 | 37 | 75 | 230 | 25 | 92 | 13 | 18 | 16 | 99 | 25 | 46 | 110 |
| Algarve | Н | 799 | 26 | 27 | 48 | 65 | 43 | 29 | 39 | 177 | 12 | 3 | // | // | // | 99 | 21 | 40 | 67 |
| | M | 480 | 4 | 2 | 21 | 40 | 23 | 8 | 36 | 53 | 13 | 89 | 13 | 18 | 16 | // | 4 | 6 | 43 |
| R.A. | HM | 653 | 17 | 13 | 38 | 24 | 22 | 22 | 36 | 152 | 5 | 50 | 10 | 14 | 4 | 29 | 7 | 32 | 47 |
| Acores | Н | 391 | 15 | 11 | 22 | 13 | 20 | 16 | 18 | 118 | 3 | 0 | // | // | // | 29 | 4 | 25 | 23 |
| Acores | M | 262 | 2 | 2 | 16 | 11 | 2 | 6 | 18 | 34 | 2 | 50 | 10 | 14 | 4 | // | 3 | 7 | 24 |
| R.A. | HM | 622 | 32 | 17 | 40 | 45 | 31 | 31 | | 89 | 7 | 49 | 5 | 13 | 12 | 37 | 6 | 8 | 62 |
| Madeira | Н | 338 | 29 | 12 | 23 | 19 | 17 | 19 | 13 | 70 | 4 | 1 | // | // | // | 37 | 5 | 7 | 32 |
| madena | M | 284 | 3 | 5 | 17 | 26 | 14 | 12 | 17 | 19 | 3 | 48 | 5 | 13 | 12 | // | 1 | 1 | 30 |

Table 5: Deaths by causes of death (ICD-10 - European short list) and gender in the country, from 1999 to 2019 (excerpt). Source: INE.

| | 4.1: Óbitos por causa de morte (CID-10 - lista europeia sucinta) e sexo, no país, 1999 a 2019 | | | | | | | | | | | | | |
|-------------------------------------|---|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|------|--|--|
| ausa de morte | Sexo | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019 | | |
| LES - 11 Tumor maligno do cólon | нм | 2 590 | 2 650 | 2 743 | 2 691 | 2 725 | 2 690 | 2 621 | 2 655 | 2 704 | 2 604 | 2 62 | | |
| | н | 1 438 | 1 514 | 1 501 | 1 538 | 1 560 | 1 528 | 1 510 | 1 480 | 1 557 | 1 473 | 1 47 | | |
| | M | 1 152 | 1 136 | 1 242 | 1 153 | 1 165 | 1 162 | 1 111 | 1 175 | 1 147 | 1 131 | 1 14 | | |
| LES - 12 Tumor maligno do reto e | нм | 1 058 | 1 114 | 1 086 | 1 122 | 1 123 | 1 118 | 1 226 | 1 254 | 1 148 | 1 216 | 1 20 | | |
| ânus | н | 669 | 712 | 675 | 702 | 677 | 672 | 789 | 757 | 716 | 747 | 74 | | |
| | M | 389 | 402 | 411 | 420 | 446 | 446 | 437 | 497 | 432 | 469 | 46 | | |
| LES - 13 Tumor maligno do figado | нм | 861 | 895 | 979 | 969 | 1 037 | 1 090 | 1 134 | 1 171 | 1 231 | 1 240 | 1 26 | | |
| e das vias biliares intra-hepáticas | н | 607 | 611 | 693 | 690 | 726 | 777 | 817 | 845 | 898 | 896 | 92 | | |
| | M | 254 | 284 | 286 | 279 | 311 | 313 | 317 | 326 | 333 | 344 | 33 | | |
| LES - 14 Tumor maligno do | НМ | 1 200 | 1 250 | 1 292 | 1 299 | 1 376 | 1 362 | 1 423 | 1 538 | 1 551 | 1 678 | 1 65 | | |
| pāncreas | н | 672 | 680 | 691 | 700 | 732 | 742 | 753 | 860 | 799 | 880 | 89 | | |
| | M | 528 | 570 | 601 | 599 | 644 | 620 | 670 | 678 | 752 | 798 | 75 | | |
| LES - 15 Tumor maligno da laringe | нм | 3 833 | 4 046 | 4 077 | 4 012 | 4 336 | 4 301 | 4 326 | 4 434 | 4 563 | 4 631 | 4 71 | | |
| e traquela / brônquios / pulmão | н | 3 076 | 3 280 | 3 242 | 3 180 | 3 462 | 3 427 | 3 326 | 3 469 | 3 537 | 3 576 | 3 56 | | |
| | M | 757 | 766 | 835 | 832 | 874 | 874 | 1 000 | 965 | 1 026 | 1 055 | 1 14 | | |

3. Problems Identified

The first problem identified regarding pancreatic cancer is that it usually presents with insidious symptoms and is often diagnosed at advanced stages thus having poor prognosis. Symptoms vary according to the location of the tumor and are relatively non-specific, such as abdominal pain, loss of appetite, weight loss, fatigue, and jaundice, the latter occurring when the tumor reaches the head of the pancreas and causes an obstruction of the biliary tract. Another problem is the lack of well-defined screening strategies for the general population: there are no readily available and highly accurate diagnostic tests that could enable massive screening of pancreatic cancer in the general population. Screening is usually performed on those who have high-risk family history of developing pancreatic cancer.

Diagnosis of pancreatic cancer includes physical examination and diagnostic imaging tests, such as abdominal ultrasound, computed tomography (CT) scan, magnetic resonance imaging (MRI), and endoscopy. Improved ultrasound and MRI techniques have increased the capacity to detect pancreatic lesions. However, these tests still have important limitations since they are unable to detect and distinguish other lesions from pancreatic intraepithelial neoplasms [16].

Considering diagnostic tests of pancreatic cancer, it is essential to identify and validate new biomarkers, preferably tested in blood samples, that have high sensitivity and specificity and that could enable accurate and early diagnosis of pancreatic cancer, even before the tumor is detected on imaging scans [17].

Recent data suggest that the potential of circulating DNA and other markers (CancerSEEK) are highly specific and relatively sensitive for the detection of pancreatic cancer both in general and high-risk populations. However, more studies on stratified high-risk groups and based on the natural history of precursor lesions are needed [16].

4. Possible Solutions - Interventions

Considering that pancreatic cancer is the seventh leading cause of death from malignant neoplasms in Portugal, strategies aimed at prevention, diagnosis, and interventions for this disease are urgently needed.

Surgery is the only potential curative treatment for pancreatic cancer and, even so, patients who undergo surgical resection have an estimated survival rate of only 10%. Better results are observed when surgical resection is combined with neoadjuvant or adjuvant chemotherapy. Interestingly, recent studies comparing the financial costs of pancreatic cancer surgery performed in high-volume versus low-volume hospitals did not show significant differences. Even though surgeries performed at high-volume hospitals have superior outcomes in terms of morbidity and mortality (Graph 3 – Appendix), management of complications, and readmission rates, a potential reduction in financial costs was not observed. This could result from a global improvement in all outcomes or from low-volume hospitals selecting less complex cases [7]. Campaigns designed to promote cancer awareness and education, such as the World Pancreatic Cancer Day, as well as other educational activities, contribute for the recognition of behavioral risks and other risk factors for pancreatic cancer. They might have a positive impact on the adoption of preventive measures by the general population. Another example of an educational activity is the program Promoção da Literacia em Saúde sobre Estilos de Vida Saudável, that promotes education on healthy lifestyle and is carried out by the Directorate-General of Health (GDS) of Portugal. Besides, the participation in different Joint Actions and in other international projects enabling financial aid for the promotion of interventions, international European benchmarking, good practices adoption, and the conduction of the Health Literacy Survey to be concluded by 2020 also contribute for raising awareness for pancreatic cancer [8]. By ensuring access to information for the scientific and medical communities, an increase in research and a greater awareness for pancreatic cancer are expected.

The implementation of Reference Centers was essential since they are highly specialized and able to provide high quality treatments using state of the art techniques and technologies. Also, these specialized centers gather more information and expertise on pancreatic cancer and can foster scientific research and promote knowl-

edge acquisition aimed at diagnosing and treating this complex disease. Thus, reference centers are vital for multidisciplinary and interdisciplinary approaches [18, 19]

There are ten official Adult Oncology Centers of Excellence in Hepatobiliopancreatic Cancer in Portugal. They are officially recognized by the Portuguese Ministry of Health and their implementation has been recommended by the National Commission for Reference Centers (Table 6 – Appendix) [20].

These centers enable the development of specific actions, such as:

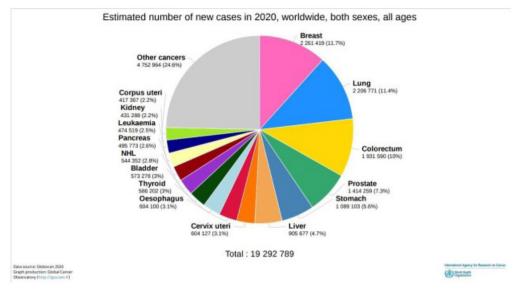
- Screening of pancreatic cancer in specific subgroups according to current practices in other European centers.
- Stimulating close collaboration of clinical and translational research teams.
- Innovating new generation complementary diagnostic tools integrated with artificial intelligence algorithms. These diagnostic

tools may facilitate the early diagnosis of pancreatic cancer as well as the development of safer and more effective surgical protocols, or new techniques, together with neoadjuvant therapy.

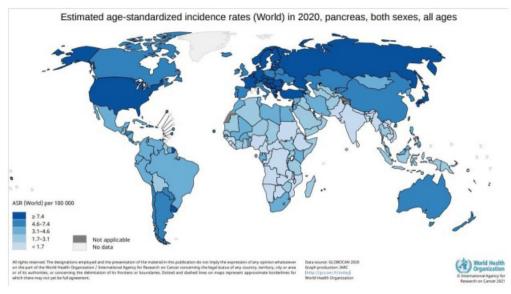
- Offering research fellowships so that studies to identify potentially relevant biomarkers for diagnostic, prognostic or therapeutic evaluation purposes can be conducted, as well as research on the reformulation of new therapeutic targets.
- Enabling access to novel therapies, such as echo-endoscopy ultrasound guided techniques to directly inject antitumor or imunnoregulatory (such as dendritic cells) agents into the tumor mass. This approach has shown promising results in patients with locally advanced pancreatic cancer.
- Providing access to a digital platform where knowledge and protocols of cooperation can be shared with several reference centers. This initiative strengthens prevention, diagnosis, and intervention processes both qualitative and quantitatively [20, 21].

Table 6: Adult Oncology Reference Centers for Hepato-Bilio-Pancreatic Cancers.

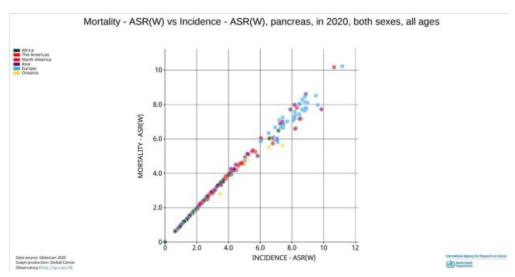
| Adult Oncology Reference Centers - Hepato-Bilio-Pancreatic Cancer: |
|--|
| Centro Hospitalar de Entre o Douro e Vouga, EPE. |
| Centro Hospitalar de Leiria, EPE |
| Hospital Santa Maria (Centro Hospitalar de Lisboa Norte, EPE) |
| Hospital Curry Cabral (Centro Hospitalar Universitário Lisboa Central, EPE) |
| Hospital Prof. Doutor Fernando Fonseca, EPE. |
| Sociedade Gestora do Hospital de Loures, S.A Hospital Beatriz Ângelo |
| Hospital Santo António (Centro Hospitalar Universitário Porto, EPE) |
| Hospital São João (Centro Hospitalar Universitário de S. João, EPE) |
| Instituto Português de Oncologia Francisco Gentil, EPE |
| Hospitais da Universidade de Coimbra (Centro Hospitalar e Universitário de Coimbra, EPE) |
| |



Graph 1: Worldwide estimation of new cancer cases, by organ, in 2020.



Graph 2 - Incidence of pancreatic cancer, by age, worldwide.



Graph 3 - Mortality .vs Incidence of Pancreatic Cancer in 2020.

5. Required Resources

In the United States, the average total cost of surgical treatments of pancreatic cancer per patient is \$61,700. This cost is higher for patients with resectable locoregional disease (\$134,700) compared with those who have unresectable locoregional or metastatic disease (\$65,300 and \$49,000, respectively) 22. In Europe, 610,000 to 915,000 quality-adjusted life years (QALYs) are lost due to pancreatic cancer [23]. There is an urgent need for financial resources directed to improving quality of life in pancreatic cancer. It seems to be a good approach to make financial investments in oncology centers.

Treatments of pancreatic and hepatobiliary cancers have evident technical advantages in reference centers compared with other centers in the United States (p < 0.001): general complications (16.5% vs. 23.6%), readmission within 90 days (26.2% vs. 30.2%), and 90-day mortality (3.0% vs. 8.7%) [7].

In Portugal, reference centers have well-defined human and technical resources established by law. They receive a minimal number of cases per year, being 20 new pancreatic cancer surgical cases (including periampullary tumors), and at least 40 Clinical Oncology cases (including metastatic disease). There are more centers available at the North and Central areas of Portugal, and service is not available at all parts of Alentejo, Algarve, or at the Autonomous Regions Madeira and Azores.

Despite the above mentioned information, we could not find official statistical data on treatment costs and the results observed. As a matter of fact, the 2019 DGS activity report [8] concluded that the maximum response time (TMRG) for surgery is not met, according to the analysis of activities carried out by the Portuguese National Health Service (SNS). Evaluations of oncology service capacity are being conducted at the SNS units. A combination of both human and technological resources is needed to standardize indicators in these reference centers thus enabling the referral of

patients diagnosed with pancreatic cancer to them in a timely manner (time between the diagnosis and the first appointment at a reference center).

By evaluating these indicators, it will be possible to assess if the Portuguese National Program for Oncological Diseases (PNDO) is adopting effective measures and meeting defined goals, as follows: a) Promotion and dynamic monitoring of screening programs in terms of efficacy, equity, and achieved health gains; b) Definition of the profile of cancer treatment centers and integration within the Portuguese cancer care system; c) Promotion of equitable access to high quality cancer treatment [24].

More studies to gather data from screening programs on the efficacy, cost-effectiveness, and impact on the morbimortality of pancreatic adenocarcinoma are needed. A randomized, prospective study to evaluate the impact on survival rates and QALYS gains in screened vs. non-screened groups is highly recommended [16].

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