Tumor markers in pancreatic cancer: a European Group on Tumor Markers (EGTM) status report

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Pancreatic ductal adenocarcinoma is one of the most difficult malignancies to diagnose and treat. The aim of this article is to review how tumor markers can aid the diagnosis and management of patients with this malignancy. The most widely used and best validated marker for pancreatic cancer is CA 19-9. Inadequate sensitivity and specificity limit the use of CA 19-9 in the early diagnosis of pancreatic cancer. In non-jaundiced patients, however, CA 19-9 may complement other diagnostic procedures. In patients with resectable pancreatic cancer, presurgical and postresection CA 19-9 levels correlate with overall survival. In advanced disease, elevated pretreatment levels of CA 19-9 are associated with adverse patient outcome and thus may be combined with other factors for risk stratification. Most, but not all, reports indicate that serial levels of CA 19-9 correlate with response to systemic therapy. Use of CA 19-9 kinetics in conjunction with imaging is therefore recommended in monitoring therapy. Although several potential serum and tissue markers for pancreatic cancer are currently undergoing evaluation, none are sufficiently validated for routine clinical use. CA 19-9 thus remains the serum pancreatic cancer marker against which new markers for this malignancy should be judged.

Key words: biomarker, CA 19-9, EGTM, guidelines, pancreatic cancer, tumor markers

Introduction

Ductal adenocarcinoma of the exocrine pancreas, commonly known as pancreatic cancer, is one of the most lethal malignancies affecting mankind (for review, see refs [1, 2]). Worldwide, in 2002, there were an estimated 232,000 new cases of pancreatic cancers and 227,000 deaths [3]. In 2006, there were ~58,000 new cases of pancreatic cancer in the European Union (EU) [4]. Although only the 13th most frequent malignancy, cancer of the pancreas was the fifth most frequent cause of cancer-related mortality in the EU [4]. At the time of diagnosis, ~20% of patients with pancreatic cancer are considered eligible for surgery and of these, about a half undergoes successful resection [5]. For these patients, the 5-year survival following participation in randomized trials that involved treatment with adjuvant chemotherapy or chemoradiotherapy was 4%–26% [6, 7]. On the other hand, for the 80% who present with locally advanced or metastatic disease, no curative therapy currently exists. These patients have median survival times of the order of 8–12 months and 5–8 months, respectively [6–8].

Overall, the annual incidence of pancreatic cancer is almost identical to its mortality rate. This poor prognosis has been attributed to failure to diagnose the disease early while the tumor may be resectable, to its propensity to disseminate and to its resistance to systemic therapies [2, 5]. Despite this poor prognosis, some advances have been made in the treatment of pancreatic cancer, in recent years. These include improvements in operative mortality and morbidity as a result of surgery in specialized centers and marginally improved outcome with the use of systemic chemotherapy [1].

Over the last two to three decades, several serum and tissue-based markers have been proposed for pancreatic cancer. The aim of this article is to review the current status of these markers. As CA 19-9 is the only widely investigated marker in pancreatic cancer [9–11], most of the article will focus on it.

CA 19-9 as a marker for pancreatic cancer

aiding diagnosis

Two large literature reviews have been carried out on the diagnostic accuracy of CA 19-9 in patients with pancreatic cancer. In 1990, Steinberg [12], following a review of the literature, identified 24 studies that compared serum CA 19-9
levels in patients with pancreatic cancer and different control groups. All these, apart from one, used 37 kU/l as cut-off point for CA 19-9. Combining data from the 24 studies, CA 19-9 was found to have an overall mean sensitivity of 81% and a mean specificity of 90% for pancreatic cancer. Increasing the cut-off point to 100 kU/l improved specificity to 98% but reduced sensitivity to 68%. At a cut-off point of 1000 kU/l, specificity was 99.8% but sensitivity was only 41%.

In 2007, Goonetilleke and Siriwardena [13] carried out a similar review of the literature focusing on studies published from 1990 to 2005. It thus included articles published since the review by Steinberg [12]. Overall, 22 studies containing a total of 2282 patients were identified in this more recent review. In this overview, the median sensitivity of CA 19-9 for pancreatic cancer was 79% (70%–90%) while the median specificity was 82% (68%–91%).

Do these findings justify the use of CA 19-9 as a diagnostic aid for pancreatic cancer? According to Steinberg [12], although CA 19-9 is not accurate enough to be recommended in screening asymptomatic subjects for pancreatic cancer, it is currently the single most useful blood test in differentiating benign from malignant pancreatic disorders. Goonetilleke and Siriwardena [13] stated that CA 19-9 should be used “in contemporary algorithms for the diagnosis of pancreatic cancer”. According to the European Group on Tumor Marker guidelines [14], CA 19-9 has limited value in the diagnosis of pancreatic cancer, especially for early forms of the disease. It may, however, complement radiological procedures, particularly in non-jaundiced patients. The National Academy of Clinical Biochemistry (NACB; USA) does not recommend measuring CA 19-9 for the diagnosis of pancreatic cancer (Sturgeon et al., unpublished data). This expert panel, however, states that if used for diagnostic purposes, the marker should be assessed in conjunction with results from other modalities such as computed tomography (CT) or endoscopic ultrasound (EUS). The NACB panel also states that appropriately interpreted CA 19-9 results can guide further invasive testing such as endoscopic retrograde cholangiopancreatography, laparoscopy or EUS fine-needle aspiration. According to the National Cancer Comprehensive Network (NCCN), “the degree of increase in CA 19-9 levels may be useful in differentiating pancreatic adenocarcinomas from inflammatory conditions of the pancreas” [15]. NCCN, however, caution that false-positive findings may occur in patients with benign biliary obstruction and false negative in subjects with Lewis a-negative genotype (see below).

Based on the above, it is clear that most expert groups cautiously recommend measurement of CA 19-9 in the initial work-up of patients presenting with suspected pancreatic cancer. The following caveats, however, should be borne in mind when using CA 19-9 as a diagnostic aid for pancreatic cancer.

• Several benign diseases including chronic and acute pancreatitis, liver cirrhosis, cholangitis and obstructive jaundice may give rise to elevated CA 19-9 levels [10–13]. In patients with cholangitis, levels of CA 19-9 in excess of 1000 kU/l have been found [16]. These elevated levels may return to normal after treatment of cholangitis and appropriate decompression of the common bile duct. In patients presenting with obstructive jaundice, levels of CA 19-9 should therefore be measured following biliary decompression [15].
• CA 19-9 can be increased in multiple types of adenocarcinoma, especially in advanced gastrointestinal cancers [10–13]. Thus, in an overview study, CA 19-9 levels were found to be elevated in 67% of 39 patients with bile duct cancer, 41% of 254 patients with gastric cancer, 34% of 664 patients with colorectal cancer, 22% of nine patients with esophageal cancer and 49% of 169 patients with hepatocellular carcinoma [12].
• CA 19-9 is not expressed in subjects with Lewis a- b-genotype. The molecules on which the CA 19-9 epitope is found is a sialylated Lewis A blood group antigen [17]. Subjects who are genotypically Lewis a- b- therefore cannot synthesize the CA 19-9 epitope. Approximately 5%–10% of the Caucasian population are believed to have this genotype. Assuming this, the maximum achievable sensitivity of CA 19-9 for pancreatic cancer in Caucasian populations is 90%–95%. Little information is available on the prevalence of the Lewis a- b- genotype in non-Caucasian populations.
• CA 19-9 lacks sensitivity for early or small-diameter pancreatic cancers. Thus, only ~50% of patients with pancreatic cancers <3 cm have elevated levels of CA 19-9 [12].
• Poorly differentiated pancreatic cancers also appear to produce less CA 19-9 than either moderately or well-differentiated cancers [12].
• Given these limitations, CA 19-9 cannot replace histological proof of pancreatic cancer in the initial diagnostic work-up, even when imaging is indicative.

determining prognosis
Multiple small-scale retrospective studies showed that newly presenting patients with elevated levels of CA 19-9 had a worse prognosis than those with low levels (for review, see ref. [18]). In one of the largest studies that evaluated the prognostic impact of CA 19-9, Ferrone et al. [19] measured perioperative levels of the marker in 176 patients with bilirubin levels <2 mg/dl. At the cut-off point commonly used in the diagnostic setting, i.e. 37 kU/l, CA 19-9 was not a significant predictor of patient outcome. Rather, the preoperative concentration of CA 19-9 that best separated patients with poor and good outcome was 1000 kU/l. Based on these findings, Ferrone et al. [19] concluded that CA 19-9 should be considered for inclusion in prognostic nomograms. According to these authors, elevated CA 19-9 levels (e.g. >1000 kU/l), in the presence of normal bilirubin levels, strongly indicate advanced disease and may justify laparoscopy, even though the lesion looks resectable for cure on preoperative imaging [19, 20]. For patients with low CA 19-9 levels and resectable lesions on preoperative imaging, the requirement for laparoscopy to detect unsuspected metastases may be decreased [19, 20].

In the study referred to above [19], postoperative levels of CA 19-9 were also associated with patient outcome. In univariate analysis, the strongest predictor of overall survival was whether marker levels declined following surgery. Of the different absolute cut-off levels investigated for prognostic impact, the strongest discrimination was found at
A concentration of 200 kU/l [19]. Using multivariate analysis, significant prognostic factors for good outcome were a postoperative CA 19-9 level <200 kU/l, a decrease in CA 19-9 levels following surgical resection as well as negative lymph nodes and low tumor stage [19].

The prognostic impact of postresection CA 19-9 levels was recently confirmed in a randomized trial investigating the use of adjuvant chemoradiotherapy [21]. In this study, CA 19-9 was used as a secondary end point. Levels greater than either 90 or 180 kU/l were found to be independent predictors of patient outcome. Surprisingly, in this study, 34% of patients were Lewis antigen negative. These Lewis antigen-negative patients, however, had a similar outcome to patients with CA 19-9 <180 kU/l.

According to the NACB guidelines (Sturgeon et al., unpublished data), serum CA 19-9 levels should be considered for risk stratification in patients with pancreatic cancer. These guidelines also state that although high concentrations are indicative of poor outcome, CA 19-9 is only one of the multiple factors that affect prognosis and treatment planning (Sturgeon et al., unpublished data). The NACB panel, however, did not indicate the level of CA 19-9 that best separated patients likely to have good and poor outcome. Indeed, as different assays for CA 19-9 give different results, the optimum cut-off point is likely to depend on the assay used, as discussed below.

**Postoperative surveillance**

One of the most frequent uses of tumor markers is in postoperative surveillance following curative surgery for a primary cancer [22]. The aim of this surveillance is to detect recurrences/metastases as early as possible. This practice is based on the assumption that the early detection of recurrent/metastatic disease and the initiation of therapy enhances the chance of cure or results in a better outcome. For most cancer types, however, a clear-cut benefit for regular surveillance remains to be established [22].

A number of studies have shown that serial determinations of CA 19-9 can detect recurrent/metastatic pancreatic cancer several months before finding clinical or radiological evidence of disease [10]. The clinical value of this lead time, however, is unclear, i.e. whether its availability impacts on patient outcome or increases quality of life [10]. Despite this, the NACB panel recommends that CA 19-9 should be used in the follow-up of patients after potentially curative surgery for pancreatic cancer (Sturgeon et al., unpublished data). The panel, however, caution that the value of initiating therapy based on rising CA 19-9 levels remains to be demonstrated. The panel did not indicate how frequently CA 19-9 should be measured or how a clinically significant increase was defined. According to the American Society of Clinical Oncology (ASCO) guidelines, CA 19-9 measurements by themselves cannot provide definite evidence of disease recurrence without confirmation by imaging for clinical findings and/or biopsy [23].

**Monitoring therapy in advanced disease**

In patients with advanced inoperable pancreatic cancer, the aim of systemic therapy is palliative. Based on a systematic review of the literature, Yip et al. [24] concluded that chemotherapy prolonged survival in patients with advanced pancreatic cancer and improved quality of life. Single-agent gemcitabine is presently regarded as the treatment of choice in this situation. In an attempt to improve efficacy, several trials have compared gemcitabine combinations with gemcitabine alone. Indeed, at least three meta-analyses/pooled analyses have analyzed outcome in these studies [8, 25, 26]. In one of these, Heinemann et al. [25] pooled data from two trials resulting in 503 assessable patients. One of these trials compared gemcitabine plus oxaliplatin to gemcitabine while the other compared gemcitabine plus cisplatin to gemcitabine. Pooled analysis showed that the combination of gemcitabine with a platinum analogue significantly improved progression-free survival and overall survival as compared with single-agent gemcitabine.

In a second meta-analysis, Bria et al. [26] combined the results from 20 trials that compared single-agent gemcitabine with gemcitabine-based combinations (n = 6296). Meta-analysis showed that while the gemcitabine–platinum combination marginally improved progression-free survival, the impact on mortality was minimal [26].

In a third meta-analysis, Sultana et al. [8] identified 19 studies that compared gemcitabine versus gemcitabine-based combinations. Overall, survival was better for the combination, with a decrease of 9% in risk of death (hazard ratio = 0.91; 95% confidence interval, 0.85–0.97). In particular, combination of platinum-based agents and capcitabine with gemcitabine performed better than single-agent gemcitabine. No additional benefit, however, was found if either irinotecan or 5-fluorouracil was combined with gemcitabine.

Evaluating response to systemic therapy in patients with locally advanced pancreatic cancer may be difficult using imaging procedures due to extensive desmoplasia and surrounding inflammatory changes [27, 28]. As a result, objective assessment of tumor response can be unreliable, imprecise and lack reproducibility. Furthermore, several new treatments such as epidermal growth factor receptor inhibitors may be cytostatic rather than cytotoxic.

Because of these difficulties, a number of investigators have attempted to use serial CA 19-9 measurements in an attempt to assess response and/or determine prognosis in patients with advanced pancreatic cancer undergoing treatment with systemic therapy [28–31]. Although different definitions of CA 19-9 response were used in the various studies (varied between 20% and 50%), most found that patients with declining marker levels, following initiation of chemotherapy, had a better outcome than those showing no decrease [28–31]. In one of the largest studies, Ko et al. [28] evaluated CA 19-9 response as a surrogate marker for clinical outcome in 76 patients with advanced pancreatic cancer receiving fixed-dose gemcitabine. A significant correlation was found between percentage of CA 19-9 decline and both overall survival and time to treatment failure. Patients with a ≥25% fall in CA 19-9 level had a significant better outcome than those not achieving this decrease. Based on this finding, Ko et al. [28] concluded that CA 19-9 measurements should be considered for possible use as a surrogate end point in clinical trials of new systemic therapies for pancreatic cancer.

In contrast to reports linking declining serial levels of CA 19-9 with response to chemotherapy, Hess et al. [32] failed to
find any significant relationship between tumor response to therapy and CA 19-9 levels (n = 175). This negative relationship was found irrespective of the magnitude of decline in CA 19-9 levels, i.e. whether it was ≥25%, ≥50% or ≥75%. Of concern was the observation that 11 of 23 patients who had progressive disease based on CT evidence displayed a decrease of ≥50% in CA 19-9 levels. In this study, however, pretreatment CA 19-9 levels were an independent predictor for survival.

The NACB panel recommends that serial measurements of CA 19-9 be used along with imaging to monitor response to therapy, especially palliative chemotherapy (Sturgeon et al., unpublished data). According to the ASCO guidelines, present data are insufficient to recommend the routine use of CA 19-9 alone for monitoring response to therapy [23]. CA 19-9, however, can be assayed at the start of therapy for locally advanced or metastatic disease and every 1–3 months during active therapy. If serial levels of CA 19-9 increase, this may indicate disease progression. Confirmation of progression should be established with additional testing. The optimum frequency of CA 19-9 testing as well as the magnitude of change in concentration that is likely to be clinically significant remains to be established (see below).

issues relating to the measurement and interpretation of CA 19-9 levels

Although assays for CA 19-9 have been available for almost 30 years, its measurement is still somewhat problematic, reflecting primarily the lack of an international standard for CA 19-9 and differences in assay design. The consequent poor comparability of CA 19-9 results obtained using different methods complicates their interpretation particularly if different assays are used to determine sequential or serial levels of the marker. The following points should thus be borne in mind when measuring CA 19-9 levels.

• Different assays may give different results [33, 34]. It is therefore important that reports of CA 19-9 levels state the method used for analysis [35].

• For patients undergoing serial monitoring, the same method should ideally be used throughout. If a method has to be changed, CA 19-9 levels should be determined in two to four serial specimens using both the old and new methods in order to establish a new baseline [35, 36].

• The cut-off point for CA 19-9 depends on the context or the question being addressed. The use of 37 kU/L appears to be the best for discriminating between benign and malignant disease [34]. For determining prognosis, the optimum cut-off point is unknown but is clearly dependent on whether the measurement is made preoperatively or postoperatively (see above). For postresection values, however, levels between 90 and 200 kU/L have been reported to supply independent prognostic information [19, 21].

• In monitoring patients, the magnitude of difference between successive levels that are clinically significant is unclear. Intraindividual biological variation and analytical imprecision studies carried out on apparently normal subjects concluded that the critical difference between sequential values of CA 19-9 was 45%–50% [37, 38]. A 40%–50% change in serial levels has therefore been suggested as indicating a significant change [37, 38]. Whether these findings in apparently healthy subjects can be extrapolated to patients with pancreatic cancer, however, is unclear.

• In patients with the Le a-b-genotype, CA 19-9 levels are not increased even in the presence of advanced pancreatic cancer [17]. For monitoring patients with this phenotype, other markers such as carcinoembryonic antigen or specific cytokeratins should be considered.

other serum markers

Several other serum markers have been proposed for pancreatic cancer (Table 1) [9, 11, 39–48]. None of these have been shown to be superior to CA 19-9 and none are widely used for clinical purposes.

tissue-based markers

K-ras

K-ras functions as a guanine nucleotide-binding protein involved in growth factor signal transduction [49]. This signaling may result in increased cell proliferation, enhanced cell survival and resistance to apoptosis. K-ras is one of the most frequently mutated c-oncogenes in human cancer. The

<table>
<thead>
<tr>
<th>Table 1. Markers proposed for pancreatic cancer but not yet in clinical use</th>
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<td>Marker (serum)</td>
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<td>CA 242</td>
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<td>TPA</td>
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<td>M2-pyruvate kinase</td>
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<td>Mic-1</td>
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<td>IGFBP-1*</td>
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<td>Du-Pan</td>
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<td>Haptoglobin</td>
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<td>Serum amyloid A</td>
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<td>Proteomics</td>
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<td>Marker (tissue)</td>
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<td>K-ras</td>
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<td>p53</td>
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<tr>
<td>Specific mucins (MUC1, 2, 5AC)</td>
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<tr>
<td>Micro RNAs</td>
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<td>p21</td>
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<td>SMAD4</td>
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<td>BCl-2</td>
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<td>Gene expression microarray</td>
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* May be of value in identifying subjects at increased risk of developing pancreatic cancer.

CEA, carcinoembryonic antigen; TPA, tissue polypeptide antigen; TPS, tissue polypeptide-specific antigen; Mic, macrophage inhibitory cytokine; IGFBP-1, insulin-like growth factor binding protein-1.
mutant form behaves as a constitutively active form of ras that is continually involved in signal transduction.

Mutations in \(K-ras\) are present in \(\sim90\%\) of pancreatic ductal carcinomas and appear to play a role in the relatively early stages of carcinogenesis [50–55]. Most of these mutations occur in codon 12, with fewer mutations in codons 13 and 61. Because of the high frequency of mutations in pancreatic cancer, \(K-ras\) has been widely investigated as a potential marker for pancreatic cancer, especially for determining prognosis.

Garcea et al. [50], following a systematic review of the literature, identified 11 studies that related mutant \(K-ras\) to outcome in patients with pancreatic cancer. Most of these studies were retrospective and insufficiently powered to establish a meaningful relationship with prognosis. Furthermore, a multiplicity of methods with varying sensitivities and specificities were used to determine mutant \(K-ras\). While some studies reported a significant association between the presence of mutant \(K-ras\) and poor outcome, others found no significant relationship. Based on available evidence, \(K-ras\) cannot be recommended at present for routinely determining prognosis in patients with pancreatic cancer.

Mutant \(K-ras\) has also been investigated as a diagnostic aid for pancreatic cancer. Indeed, the mutant gene has been detected in pancreatic juice, blood and stools from patients with pancreatic cancer [51–55]. Its diagnostic ability in these fluids, however, is limited by its lack of sensitivity and specificity, i.e. similar mutations can occur in pancreatitis, putative precursor lesions for invasive pancreatic cancer and in other cancer types.

\(p53\)

The \(p53\) tumor suppressor gene encodes a transcription factor that regulates the expression of genes involved in apoptosis, angiogenesis, cell cycle and genome maintenance [50, 56–58]. It is the most frequently mutated gene in human cancer. Mutations in the \(p53\) gene are found in \(\sim50\%\) to \(70\%\) of pancreatic cancers [50]. In contrast to \(K-ras\) mutations, mutations in \(p53\) appear to be formed relatively late in the genesis of pancreatic cancer.

In their systematic review of the literature, Garcea et al. [50] identified 16 studies that related \(p53\) mutation/overexpression to outcome in patients with pancreatic cancer. These studies suffer from the same limitations as mentioned above for mutant \(K-ras\). As with mutant \(K-ras\), conflicting data also exist on the relationship between \(p53\) status and patient outcome.

\(\text{mucins}\)

Mucins are large membrane or extracellular proteins that are heavily glycosylated with complex oligosaccharides [66]. A structural feature that is common to all mucins is the tandem repeat domains that are rich in serine, threonine and proline residues. Some of the best-known tumor markers are mucins. Thus, the CA 125 assay measures MUC16, while the CA 15-3 assay detects MUC1. Indeed, the CA 19-9 assay detects a sialylated lacto-N-fucopentanose II sugar that is part of mucin-like molecules [10, 11].

Considerable evidence indicates that mucins play a role in the formation and progression of cancer [59, 60, 66]. MUC1 and 4, in particular, have been implicated in the formation of pancreatic cancer [59, 60]. It is therefore not surprising that mucins have been investigated as possible markers for this malignancy.

In 2007, Wang et al. [61] investigated the potential value of specific mucins in differentiating pancreatic cancer \((n = 40)\) from benign pancreatic tissue \((n = 16)\). Compared with cytology alone, the combined measurement of MUC1 plus cytology and MUC5AC plus cytology provided significantly higher sensitivity (85\% versus 65\%, 100\% versus 65\%) and accuracy (89\% versus 73\%, 91\% versus 72\%) for pancreatic cancer. The combination of MUC2 plus cytology and MUC5AC plus cytology yielded higher sensitivity (78\% versus 39\%, 100\% versus 39\%) and specificity (97\% versus 60\%, 71\% versus 60\%) for mucinous tumors than cytology alone.

Measurement of these mucins might thus be of value in aiding the diagnosis of pancreatic cancer, especially if they could be detected in serum.

\(\text{micro RNAs}\)

Micro (mi)RNAs are small non-protein-coding RNA (\(\sim22\) nucleotides) molecules that negatively regulate gene expression at the posttranscriptional level [62]. Recent evidence indicates that specific miRNAs contribute to cancer formation and progression [62]. miRNAs may play a role in cancer by regulating the expression of c-oncogenes and tumor suppressor genes or by acting as oncogenes or tumor suppressor genes.

Similar to the situation with mucins, miRNAs have been investigated for their ability to differentiate between benign and malignant pancreatic tissue. Using RT–PCR, Lee et al. [63] measured the expression of \(>200\) miRNAs in pancreatic adenocarcinomas \((n = 28)\), paired benign tissue \((n = 15)\), normal pancreatic tissue \((n = 6)\), chronic pancreatitis \((n = 4)\) and pancreatic cell lines \((n = 9)\). Based on the expression of these RNA species, the authors were able to differentiate cancer from normal pancreas, pancreatitis and cell lines. Use of a specific algorithm correctly classified all 28 cancers, all six normal pancreases and 11 of 15 adjacent benign tissues.

Bloomston et al. [64] also used miRNA expression to differentiate benign from malignant pancreatic tissue. Twenty-one miRNAs with increased expression and four with decreased expression correctly differentiated pancreatic cancer \((n = 65)\) from normal pancreatic tissue in 90\% of the cases. Fifteen overexpressed species and eight underexpressed miRNAs distinguished pancreatic cancer from chronic pancreatitis, with 93\% accuracy.

As well as being potentially useful in pancreatic cancer diagnosis, miRNAs may also be of value in predicting patient outcome. Six miRNAs were differentially overexpressed in patients with long-term survival compared with those who died within 24 months of diagnosis [64]. One miRNA was particularly predictive of outcome, i.e. miR-196a-2. Patients having tumors with elevated expression of miR-196a-2 had a median survival of 14.3 months compared with 26.5 months for those with low expression \((P = 0.009)\).

\(\text{other tissue-based markers}\)

Other potential tissue-based markers for pancreatic cancer are listed in Table 1.
conclusions

Although discovered ~30 years ago, CA 19-9 remains the gold standard serum marker for patients with pancreatic cancer. While some expert panels recommend measurement of CA 19-9 in the diagnostic work-up of patients with pancreatic cancer (Sturgeon et al., unpublished data) [14, 15], lack of specificity and sensitivity limits its use in this setting. Increasing evidence indicate that CA 19-9 may serve as a prognostic marker in the perioperative evaluation of patients with pancreatic cancer. Specifically, high postoperative CA 19-9 levels have been associated with poor survival and may identify patients who should receive alternative systemic therapy or be entered into clinical trials evaluating new treatments for pancreatic cancer. Serial CA 19-9 levels may be combined with imaging in evaluating efficacy in patients undergoing treatment of advanced pancreatic cancer. As mentioned above, in this situation, it is important to use the same CA 19-9 assay throughout.

Future research in pancreatic cancer should focus on markers for the identification of subjects at increased risk of developing this malignancy, the development of sensitive and specific markers for its early detection and the discovery of markers for selecting patients likely to respond to specific therapies. This last point is particularly important for the new biological therapies currently undergoing evaluation for the treatment of pancreatic cancer.

A starting point for the identification of new biomarkers for pancreatic cancer could be a recent report by Jones et al. [69]. These authors carried out a comprehensive global gene analysis on 24 pancreatic cancers. This involved sequencing 23 219 transcripts as well as a detailed identification of amplifications and homozygous deletions. The pancreatic cancers investigated contained on an average 67 genetic alterations, most of which were point mutations. These alterations involved a core group of 12 signaling systems and processes that were altered in 67%–100% of the cancers. Over 500 genes were at least 10-fold overexpressed in >90% of the cancers. Fifty-four of these genes encoded proteins that were predicted to be secreted or overexpressed on the cell membrane. These overexpressed proteins should provide a valuable resource for identifying new markers as well as new therapeutic targets for patients with pancreatic cancer. Thus, for the first time, we can now rationally start to identify new markers as well as therapeutic targets for pancreatic cancer.

references


